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CHEMISTRY 435 I SEMESTER 1957-58

POLYCYCLIC AROMATIC HYDROCARBONS. CHEMICAL STRUCTURE AND CARCINOGENIC ACTIVITY

Reported by John R. Rogers September 16, 1957

INTRODUCTION

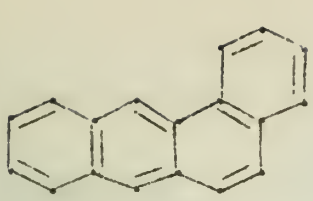
For many years several polycyclic aromatic hydrocarbons have been known to possess carcinogenic activity, but the reactions leading to carcinogenesis are not yet fully understood. Correlations between chemical reactivity and carcinogenic activity have been made and were found to be useful in suggesting possible modes of carcinogenesis. Especially helpful now is the use of C^{14}-labeled carcinogens to follow the metabolic processes occurring with these compounds in test animals.

This subject was covered rather briefly in an earlier seminar (1). Because the subject is broad, this seminar will primarily be concerned with the work carried out using 3,4-benzpyrene and especially 1,2,5,6-dibenzanthracene.

CARCINOGENIC HYDROCARBONS FROM HIGH TEMPERATURE TARS

The first relationship between skin cancer and coal tar was provided in 1915 by Yamagiwa and Ichikawa when they induced cancerous growths on rabbits' ears by the application of coal tar (2). Carcinogenic coal tar fractions were observed to have characteristic fluorescence spectra, all of which had major bands at 4000, 4180 and 4400 A (3). 1,2-Benzanthracene (1,2-BA, I), only recently proven to be a weak carcinogen (4), had a fluorescence spectrum similar to that of the carcinogenic fractions. This compound was then found to be noncarcinogenic, but in 1930 Kennaway and Hieger showed that 1,2,5,6-dibenzanthracene (1,2,5,6-DBA, II) could induce tumors in experimental animals (5). Final proof that polycyclic aromatic hydrocarbons were the carcinogenic agents in coal tar was presented in 1933 when Cook et. al. isolated 3,4-benzpyrene (3,4-BP, III) from the tar and found that its fluorescence spectrum was identical with that of the more carcinogenically active fractions (6).

Kennaway (7,8) showed that the formation of carcinogenically active tars from coal, petroleum, acetylene, and isoprene was entirely dependent on the temperature to which the starting materials were heated: tars obtained at successively higher temperatures showed an ascending order of potency. For example, isoprene tar formed at 800°C and coal tar formed at temperatures above 560°C were very carcinogenic. More recently the whole tar recovered from cigarettes smoked in a way to reproduce human smoking was found to be carcinogenic; and studies which are still being carried out show that carcinogenic hydrocarbons are present in unsmoked tobacco and paper, but that the amounts of these compounds increase considerably on smoking (9-13). Pyrolysis of the tobacco and paper at temperatures of 650 to 900°C undoubtedly causes the formation of carcinogenic hydrocarbons, possibly from terpenes or paraffins present in the original materials (10,13). Some of these hydrocarbons which have been identified are 3,4-BP (III), 1,2-BA (I), and 1,12-benzperylene (IV) (10,13-18).



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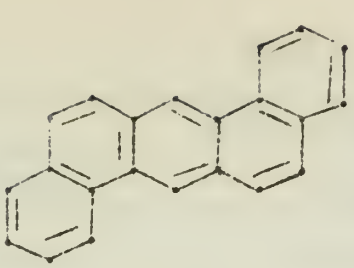

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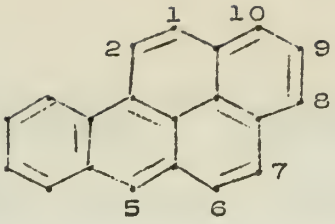

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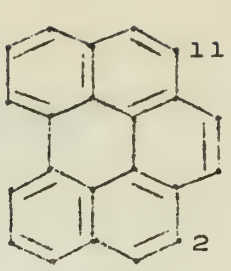
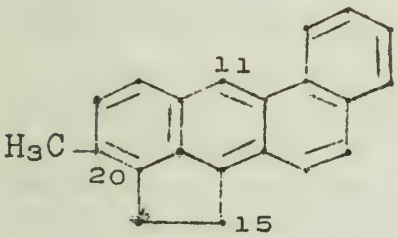


IV

CHEMICAL STRUCTURE AND REACTIVITY

A common structural feature of these carcinogens is an underlying phenanthrene nucleus substituted in certain positions by methyl groups or condensed benzene rings (19,20). This is easily seen in the compounds already mentioned and in the following series of compounds: 20-methylcholanthrene (V), 9,10-dimethyl-1,2-BA (VI), and 1,2,3,4-tetramethylphenanthrene (VII).



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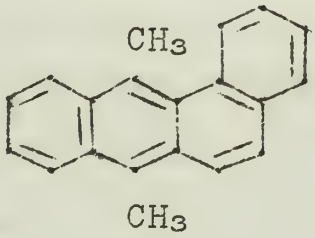
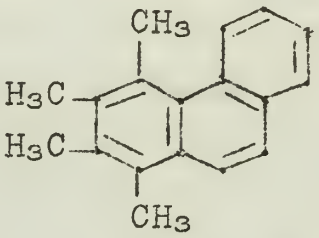
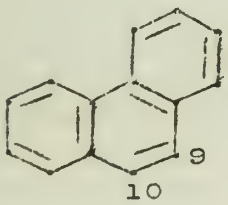


VI

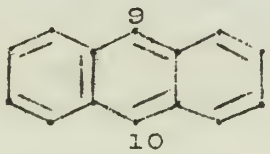


VII

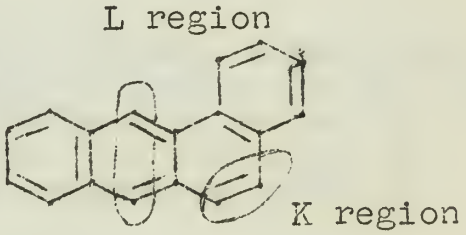
The carcinogenically active compounds studied have one or more bonds or carbon atoms at which addition or substitution reactions occur readily. For example, the 9,10-bond in phenanthrene (VIII) behaves more like an ethylenic double bond than an aromatic one; and the 9 and 10 positions in anthracene (IX), too, are quite reactive, being able to undergo both addition and substitution reactions (21). These two reactive regions are combined in 1,2-BA and have been labeled the K and L regions by the Pullmans (22) (see figure X).



VIII



IX



X

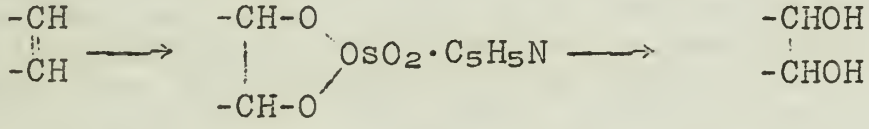
Considerable work has been done in attempts to correlate the chemical reactivity of these compounds with their carcinogenic activity. Fieser and his co-workers found such a relationship, which was only approximate, using certain reagents. Substitution reactions with lead tetraacetate (23,24) and thiocyanogen (25) indicated a general increase in the chemical reactivity with an increase in carcinogenic activity of the compounds tested: (in general order of increasing reactivity) 1,2,5,6-DBA < anthracene < 1,2-BA < 3,4-BP < 20-methylcholanthrene. These substitutions were found to occur at or near the L region; but the results obtained were not conclusive, for 1,2,5,6-DBA is a stronger carcinogen than 1,2-BA. For experimental results see Table I.

TABLE 1

Compound	Positions attacked	Lead tetraacetate Yield	Thiocyanogen Yield
Anthracene	9 and 10	40-50%	45%
1,2-BA	10 9 (mixture)	52%	8% 5% 58% (crude)
1,2,5,6-DBA	?	No homogeneous reaction product isolated	No homogeneous reaction product isolated
3,4-BP	5	94%	82%
20-methyl-cholanthrene	15	46%	89%

The reactivity towards maleic anhydride decreases in the series anthracene > 1,2-BA > 1,2,5,6-DBA > 20-methylcholanthrene, and there is essentially no reactivity with 3,4-BP (26-28). This decrease of reactivity of the L region towards cyclic dienophile additions corresponds reasonably well to a progressive increase in carcinogenic activity, except that 20-methylcholanthrene is a stronger carcinogen than 3,4-BP.

Recently, much more significant results have been obtained using Criegee's reagent (osmium tetroxide in the presence of pyridine), which adds preferentially to reactive bonds. This reagent gives complexes which on mild hydrolysis yield the corresponding cis-diols:



In polycyclic hydrocarbons the reaction, when it occurs, takes place at the reactive K region. A quantitative study by Badger (29,30) has shown the following order of increasing reactivity in a series of representative compounds: phenanthrene < pyrene < 1,2-BA < 1,2,5,6-DBA < 3,4-BP. The order runs parallel to the increasing order of carcinogenic activity.

Two fundamental propositions presented by Pullman (31) as a result of the above information are that the appearance of carcinogenic activity in aromatic hydrocarbons is determined by the existence of an active K region, and if the molecule also contains an L region it should be rather inactive. For example, 3,4-BP has no L region, but only a reactive 5-carbon, and is very strongly carcinogenic, while 1,2,5,6-DBA has two possible K regions as well as an exposed L region and is a considerably weaker carcinogen.

ELECTRONIC STRUCTURE AND CARCINOGENIC ACTIVITY

Quantum mechanical studies of the electronic structure of the polycyclic aromatic hydrocarbons have been carried out with the resulting assignment of certain indexes to the various bonds and

carbon atoms present. Several articles cover the theories involved and they will not be discussed in detail here (32-34). The localization theory, a theory of chemical reactivity based on a set of indexes which describe the reacting molecule, is now fairly well accepted. The basic theoretical indexes of this theory are the carbon localization energy (C.L.E.) (35), bond localization energy (B.L.E.) (36,37), and para localization energy (P.L.E.) (38): C.L.E. is the difference in resonance energy between the initial hydrocarbon and the hydrocarbon polarized in such a way that two, one or no π electrons are located at the attacked position, depending on the type of reaction occurring; and the localization energy of any carbon is independent of the nature of the localization assumed. B.L.E. is the amount of energy needed to disturb the electronic structure of a conjugated molecule so that a pair of π electrons (a double bond) are localized between two adjacent carbon atoms. It is thus the difference in resonance energy between the original molecule and the conjugated fragment which remains when the bond in question is removed from conjugation. P.L.E. is the amount of energy needed to perturb the electronic structure of a conjugated molecule so that two π electrons are localized at para positions, one with respect to the other. This energy, too, is the difference in resonance energy between the original molecule and the remaining conjugated fragments.

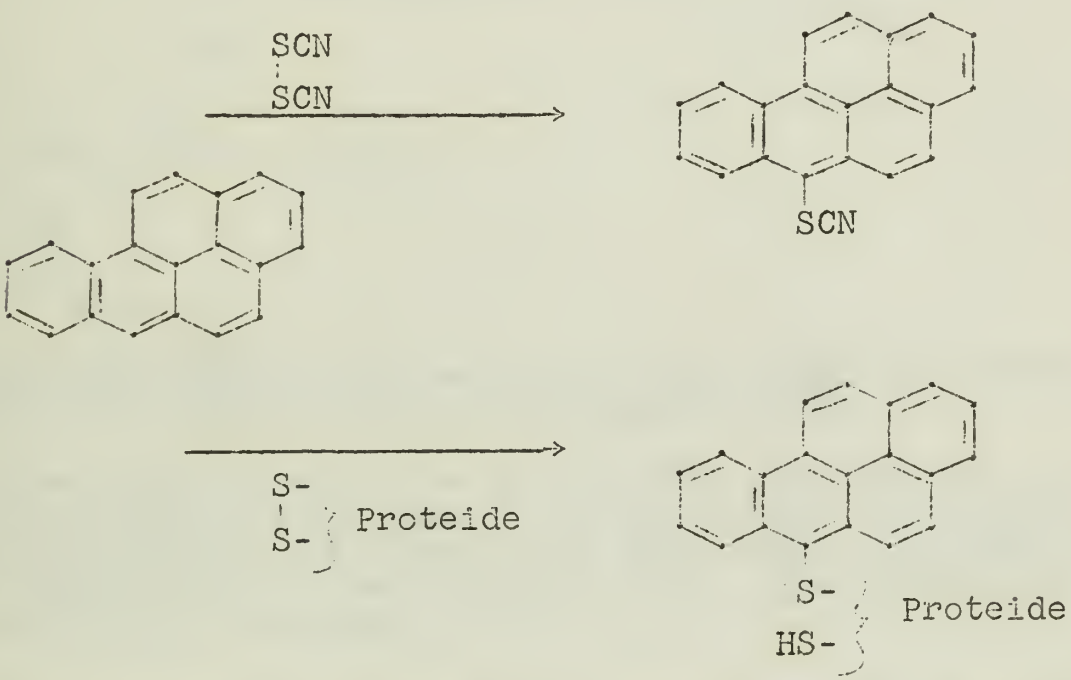
The bond and para localization energies are quantities suitable for measuring the ease of addition reactions occurring at a bond and at 1-4 positions of a conjugated system. But these simple indexes are sometimes insufficient, for the localization energies of the 3-4 bond of 1,2-BA and the 6-7 bond of 3,4-BP are practically the same, while the addition of OsO_4 takes place more rapidly in BP than in BA at the bonds mentioned. The Pullmans (31) have resolved this difficulty by using complex indexes to describe these bonds: A combination of the B.L.E. and C.L.E.(min.) is more suitable for describing a certain bond than the B.L.E. alone. C.L.E.(min.) is defined as the minimum value of localization energy calculated for one of the two carbon atoms of a particular bond. P.L.E. plus C.L.E. (min.) is similarly effective for a para region. In carcinogenic hydrocarbons the K region is the bond which has the smallest value for B.L.E. + C.L.E.(min.), and the L region, when one is present, has the smallest P.L.E. + C.L.E.(min.). But to be carcinogenic the complex index of the K region should be small and that of the L region should be large. For data concerning numerical limits see Table II. ($\beta \sim 20$ kcal/mole).

TABLE II

Compound	K region Bond	K region B.L.E.+C.L.E. (min.)	L region Carbons	L region P.L.E.+C.L.E. (min.)	Carcinogenic activity
1,2-BA	3-4	3.29β	9,10	5.53β	+
1,2,7,8-DBA	3-4	3.31β	9,10	5.66β	+
1,2,5,6-DBA	3-4	3.30β	9,10	5.69β	++
2,3,5,6-dibenzphenanthrene	9-10	3.30β	1,4	5.48β	-

MECHANISMS OF CARCINOGENESIS

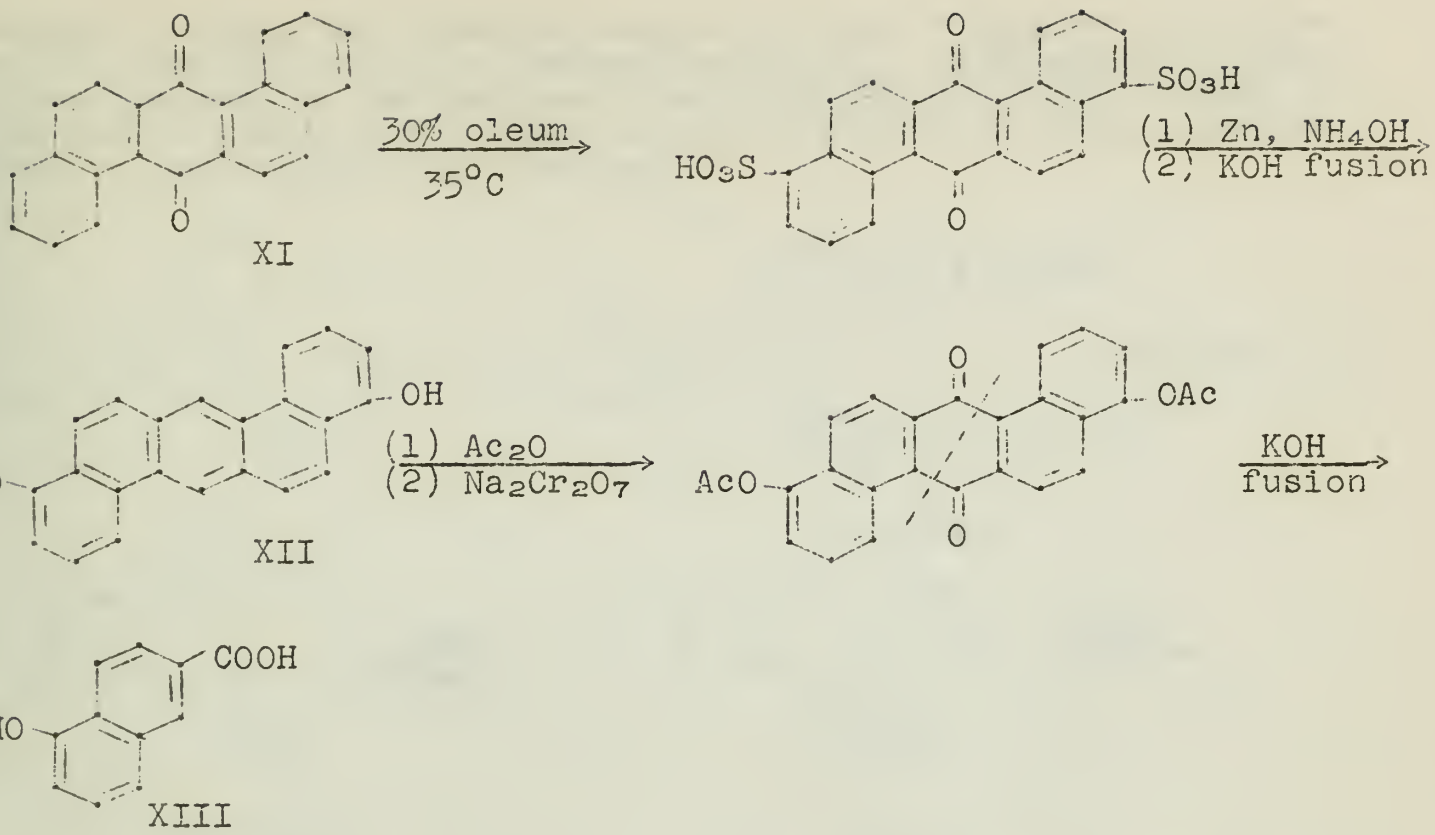
For many years most workers have believed that carcinogenesis is related to chemical binding between the carcinogenic material and cell constituents within the body. The exact nature of such combination is still not known, but an early suggestion by Fieser (24) was that an -S-S- bond of a protein or peptide is broken with the formation of a free sulfhydryl group and a hydrocarbon-peptide link. On the basis of experimental work completed with thiocyanogen (25), he postulated that a similar reaction occurs *in vivo*,



thus interferring with the sulfur metabolism of, perhaps, some peptide hormone. The reaction he postulated would involve the L region, and the reactive K region would take no part.

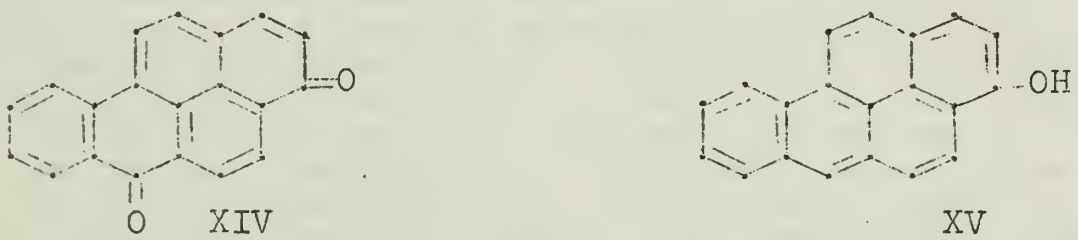
The first clear demonstration of the interaction of a carcinogenic hydrocarbon with tissue constituents was given by Miller in 1951 (39), who recovered protein-bound derivatives of 3,4-BP from the epidermis of mice following application of the hydrocarbon. *In vitro* applications of 3,4-BP to the skin of freshly killed mice did not produce any such binding. The bound derivatives were broken down into two fractions only by strong alkaline hydrolysis, indicating that chemical binding had occurred. The hydrocarbon fraction was not identified, nor could the site at which binding occurred be determined.

In 1940, Dobriner *et.al.* (40) isolated from the eliminations of test animals a metabolic product of 1,2,5,6-DBA, which Fieser and Cason (41) subsequently identified as the 4',8'-dihydroxy derivative (XII). Starting with 1,2,5,6-dibenz-9,10-anthraquinone (XI), they made the dihydroxy compound and proved its structure by acetylation, oxidation to the quinone, and potassium hydroxide fusion to 5-hydroxy-2-napthoic acid (XIII):

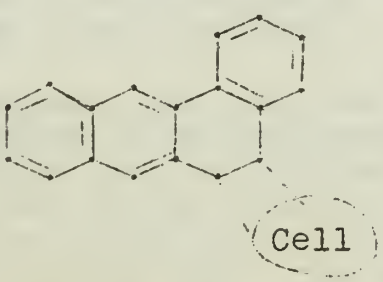


The dihydroxy derivative, believed to be formed by a detoxication process, was found to be non-carcinogenic (42).

Some elimination products of 3,4-BP isolated and identified were 3,4-BP-5,8-quinone (XIV) and 8-hydroxy-3,4 BP (XV) (43,44). The 8-hydroxy derivative was found to be only feebly carcinogenic on prolonged application to test animals (45). The quinone was not tested for carcinogenic activity.

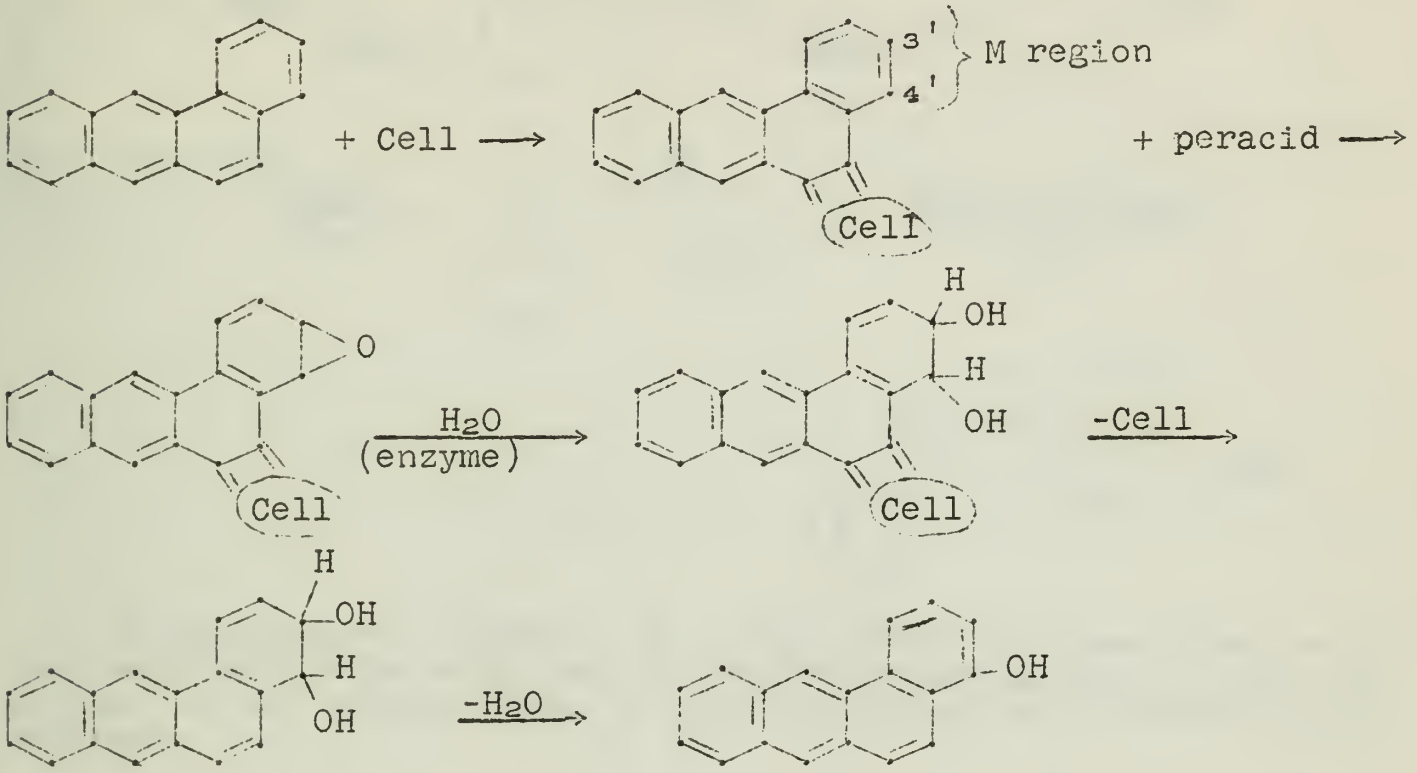


Since none of the metabolites recovered indicated that any reaction occurred at the reactive K region, Boyland (46,47) suggested that this phenomenon could be explained by the hypothesis that metabolic perhydroxylation takes place at positions other than the reactive K bond because this bond is already engaged in a different reaction with the cell:



No evidence was found concerning the type of bonding which might occur. The Pullmans assume, with no evidence to substantiate their

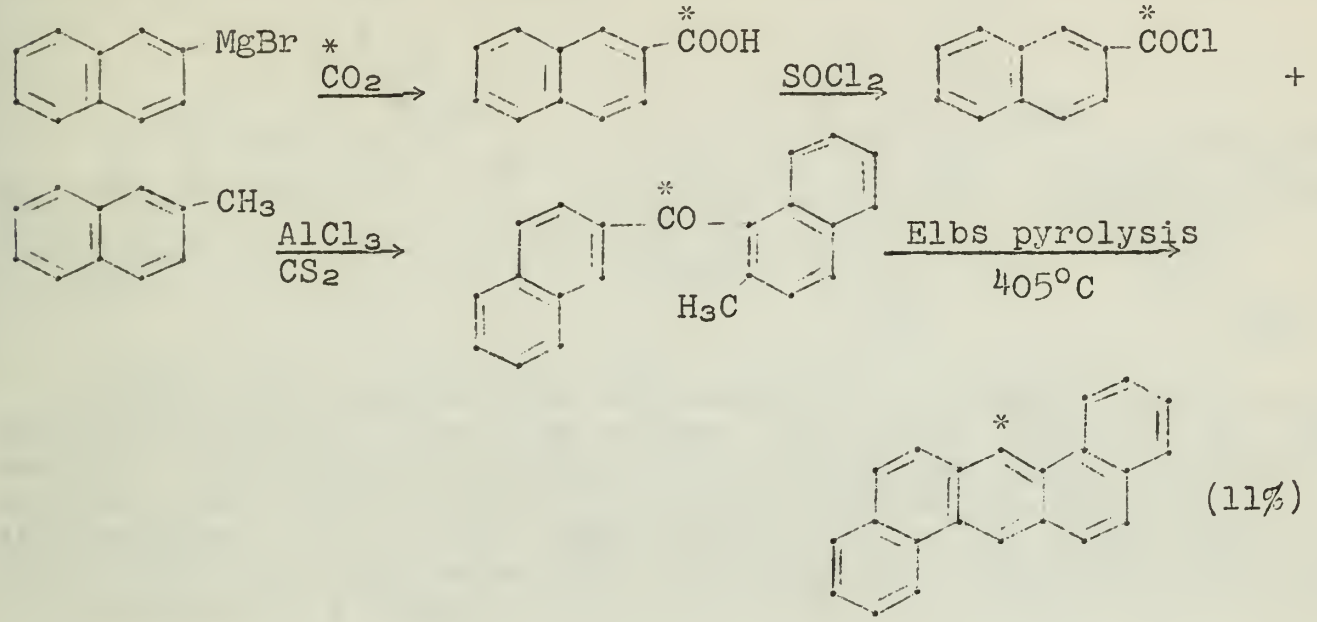
assumption, that the addition complex of the hydrocarbon with the cell was equivalent to an ortho-quinone (31). Elaborating on Boyland's hypothesis they proposed the following mechanism for the metabolic reaction which leads to the formation of hydroxy derivatives of carcinogenic hydrocarbons:



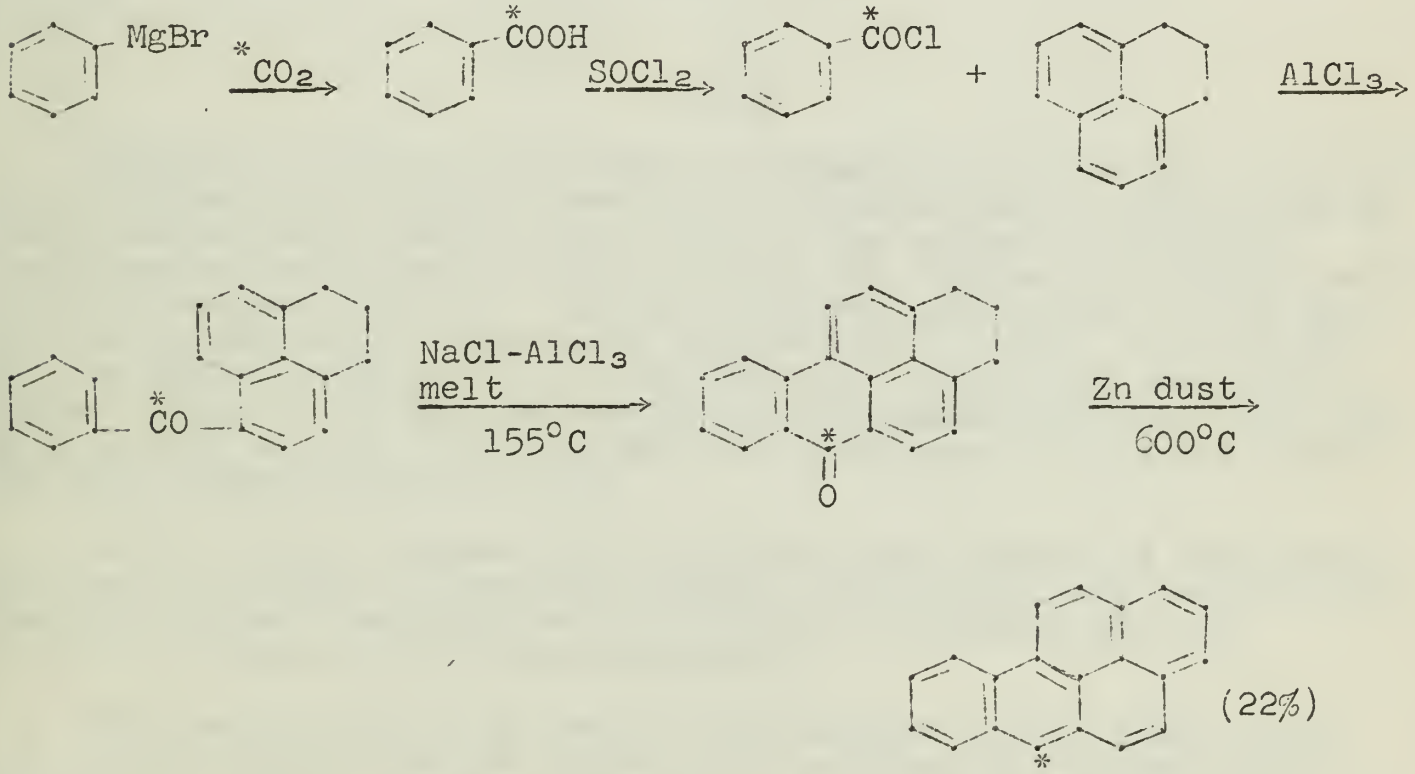
Their reasoning for the above reactions is as follows: Since the metabolic diols of anthracene recovered from rodent eliminations by Boyland have the trans configuration, the most probable mechanism for their formation is either a direct attack by free OH radicals or a hydrolysis of an intermediate epoxide. In the bound hydrocarbon attack would occur at a bond of secondary reactivity (the M or metabolic perhydroxylation region). According to their calculations perhydroxylation by OH radicals would most likely take place at the L region of the hydrocarbon, for this region conserves in the ortho-quinone the highest free valencies. But their calculations do support perhydroxylation through an intermediate formation of an epoxide, as this may be brought about the electrophilic reagents such as peracids. The primary attack would be at the 3' carbon, which in the ortho-quinone was calculated to have the greatest concentration of electrical (negative) charge (binuclear carbons excepted); and the epoxide would be formed at the 3'-4' bond, which was calculated to have more double bond character than the 3'-2' bond. Enzymatic hydrolysis of an epoxide would yield the trans diol; and dehydration of the diol would lead to the formation of the 4'-hydroxy derivative, the 4' carbon having in the initial molecule a free valence higher than the 3' carbon.

The use of carcinogenic hydrocarbons labeled with radioactive carbon (C^{14}) was introduced by Heidelberger in 1947 (48) and has proved to be a very useful tool to follow the metabolism of these carcinogens in the bodies of test animals. Synthesis of 1,2,5,6-DBA-9-C^{14} was carried out according to the synthesis of 1,2,5,6-DBA developed by Fieser and Cason (49). The method of incorporation of isotopic carbon dioxide into organic compounds by means of a Grignard reaction was developed by Dauben, Reid, and Yankwich (50).

Isotopic carbon dioxide was generated from radioactive barium carbonate by the addition of sulfuric acid. Elbs pyrolysis of the labeled ketone, 1-(2-napthoyl)-2-methylnapthalene, gave the desired product:

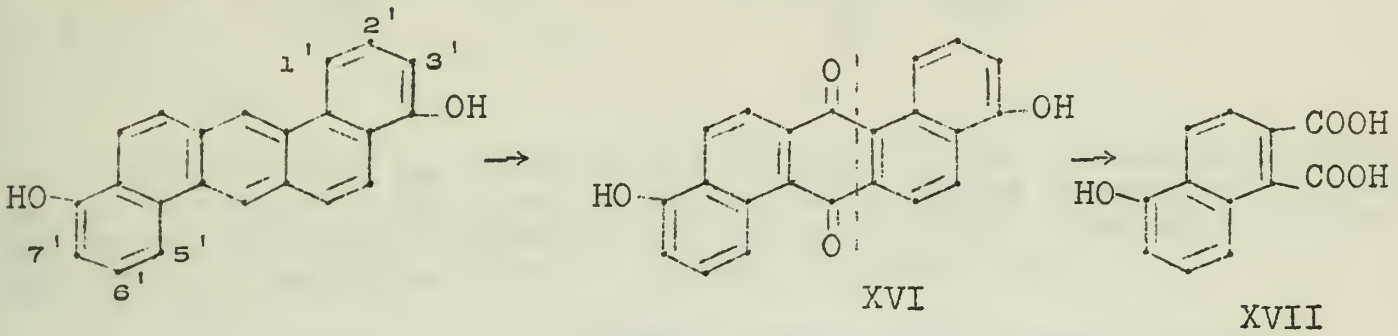


Heidelberger's synthesis of 3,4-BP-5-C^{14} (51) was based on the synthesis of 3,4-BP conducted by Fieser and Hershberg (52) and involves, as the primary step, a Scholl cyclization of 3-benzoylperinapthane:



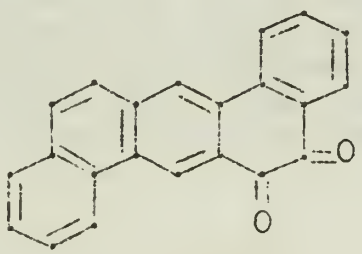
With this useful tool Heidelberger has been able to follow quantitatively the metabolism of these labeled carcinogens in test animals, and his results are now beginning to reveal why they may be able to disrupt normal cell growth. Originally he observed that after intravenous injection of test animals with these carcinogens, radioactivity remained at the site of injection for many months (51,53,54). One of the first metabolites of 1,2,5,6-DBA identified

was 5-hydroxy-1,2-napthoic acid (XVII), which comprised about eight percent of the acidic radioactivity derived from carboxyl groups from carbons 9 and 10 (55). Oxidation and unsymmetrical cleavage of the 4',8'-dihydroxy-1,2,5,6-DBA, as suggested by Dauben and Tanabe (56), was thus shown to occur:



XVI XVII

Three other metabolites of labeled 1,2,5,6-DBA, quinones retaining the intact five ring system, were later found in very small amounts. They are 1,2,5,6-dibenz-9,10-anthraquinone (XI), the 3,4-anthraquinone (XVIII), and 4'8'-dihydroxy-1,2,5,6-dibenz-9,10-anthraquinone (XVI) (57). The 3,4-quinone is the first metabolite identified which indicated that any metabolic oxidation could occur at the reactive K region.

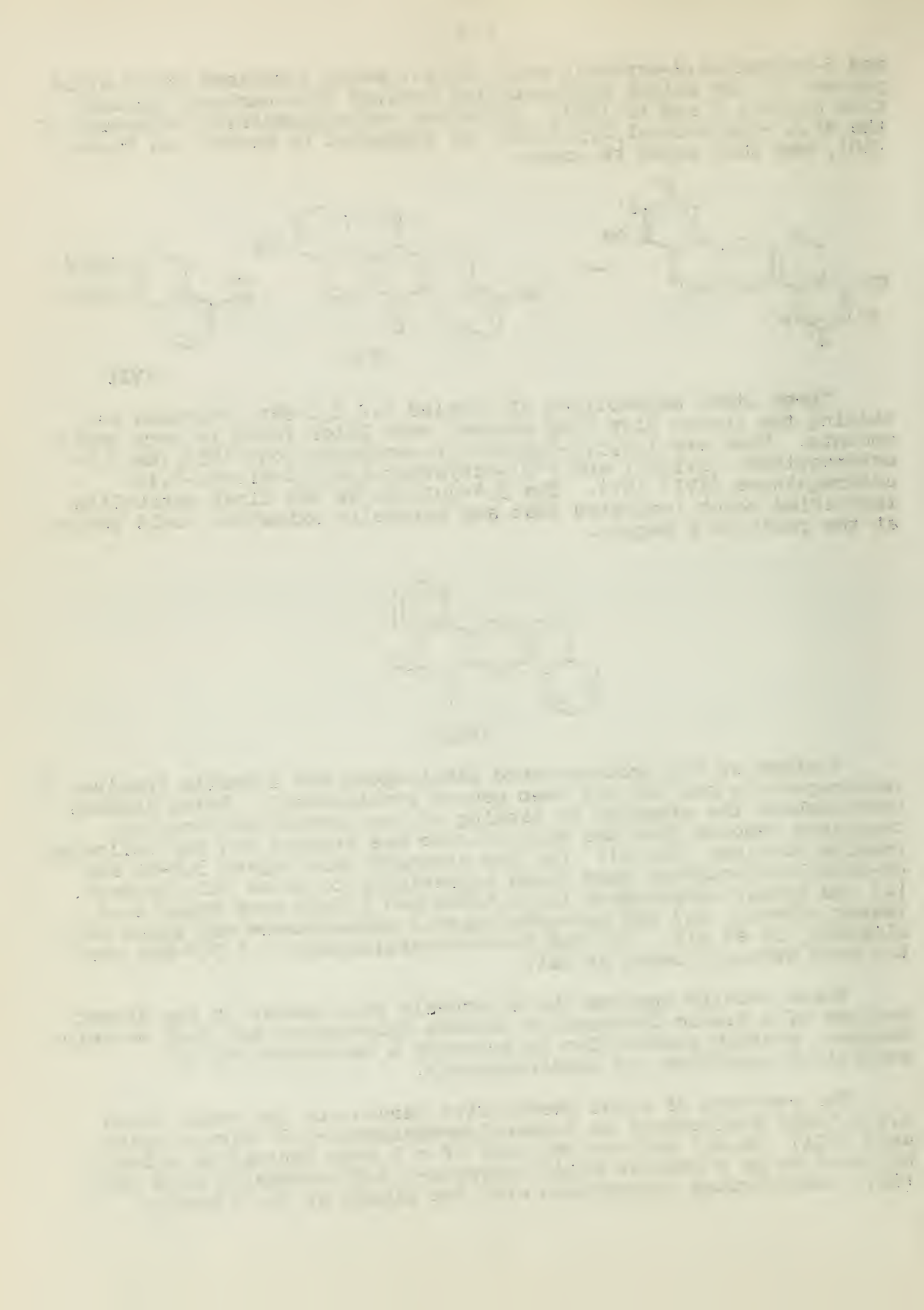


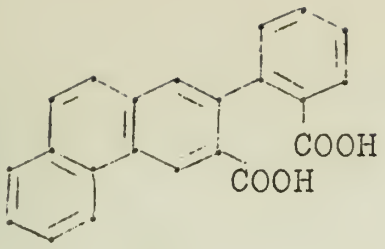
XVIII

Whether or not protein-bound carcinogens are actually involved in carcinogenesis has not yet been proven conclusively. Using labeled hydrocarbons the strength of binding of the protein-hydrocarbon complexes removed from the skin of mice was studied and the following results obtained (58,59): (a) The stronger carcinogens 3,4-BP and 20-methylcholanthrene were bound appreciably to mouse skin protein. (b) The weaker carcinogens 1,2,5,6-DBA and 1,2-BA were bound to a lesser extent. (c) The non-carcinogenic phenanthrene was bound only slightly, if at all. (d) But the non-carcinogenic 1,2,3,4-DBA was the most strongly bound of all.

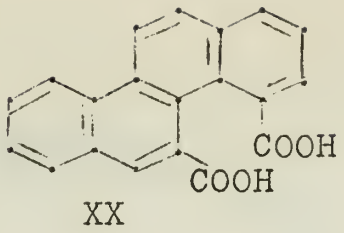
These results opposed the hypothesis that cancer is the direct outcome of a simple interaction between hydrocarbon and cell protein. However, protein combination is probably a necessary but not sufficient condition for carcinogenesis.

The recovery of about twenty-five percent of the total bound 1,2,5,6-DBA derivatives as 2-phenylphenanthrene-3,2'-dicarboxylic acid (XIX) (60,61) and the recovery of a 3,4-BP derivative which is believed to be a similar acid, chrysene-4,5-dicarboxylic acid (XX) (62), demonstrates interaction with the tissue at the K region.





XIX

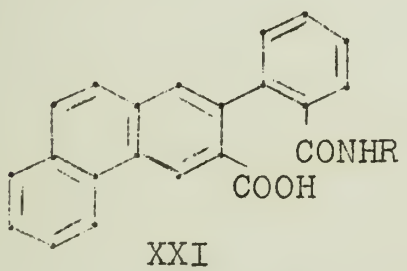


XX

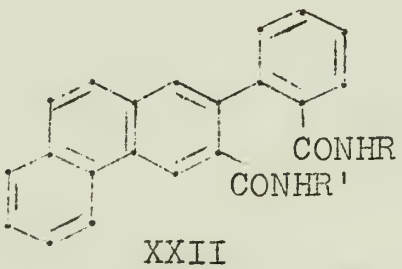
The recovered acid derivative of 1,2,5,6-DBA (abbreviated as PDA) is now believed to be bound to the protein partly through the diamide and partly through a monoamide of the acid (63). Treatment of one of the peptide fractions by the following scheme (64)

$$ArCONHR \xrightarrow{PCl_5} ArCCl{=}NR \xrightarrow[HCl]{SnCl_2} ArCH{=}NR \xrightarrow{H_2O} ArCHO + RNH_2$$

rendered twenty percent of the radioactivity extractable, half of which was acidic and the other half neutral. By this scheme if binding involved an amide linkage, the final product of these reactions would be a mono- and/or dialdehyde of PDA, which would be extractable in organic solvents. If the initial binding were through an imide or an ester linkage, cleavage of the PDA-protein bond would not be possible and no radioactivity would appear in organic solvents. The acidic fraction consisted entirely of PDA, which was presumably obtained by oxidation of the monoaldehyde, derived from a PDA-protein complex of structure XXI. The neutral fraction was probably due to the dialdehyde, obtained from a PDA-protein complex of structure XXII.

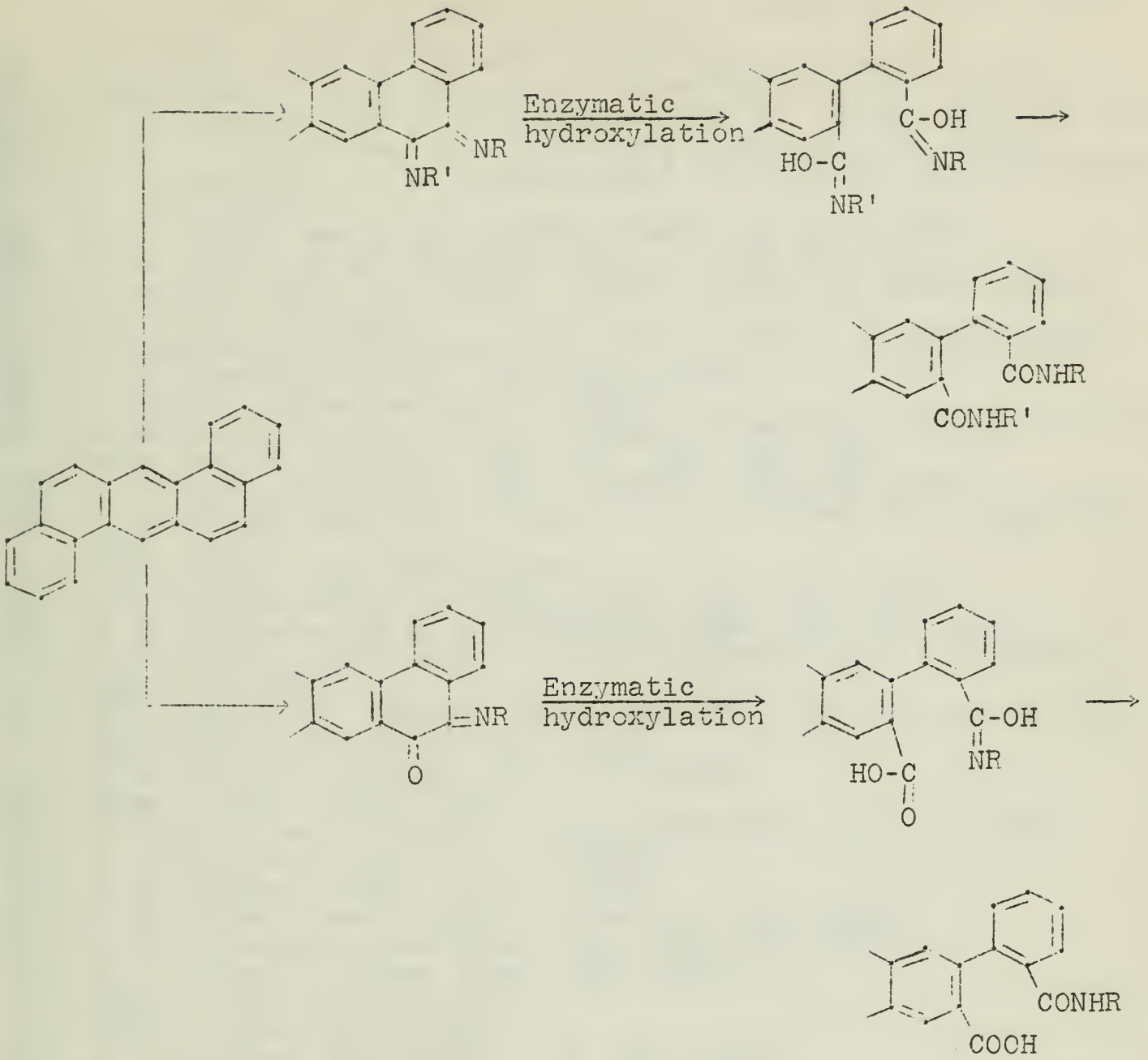


XXI



XXII

On the basis of the information they obtained, these authors suggested that the reactions in vivo might involve the intact 1,2,5,6-DBA ring system as indicated below. But there is no direct evidence of this yet.



This scheme is in accordance with the theoretical speculations of the Pullmans (31) with respect to a quinonoid bond between the hydrocarbon and the tissue. Since only twenty-five percent of the bound radioactivity has been recovered, the structure of the other seventy-five percent is not known. Possibly such a reaction as postulated above could initiate uncontrollable cell growth, or the unrecovered bound hydrocarbon could initiate cancer. Recovery of the remaining bound radioactivity will probably clarify this problem considerably.

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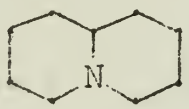
SYNTHESES OF OXYGENATED LUPIN ALKALOIDS

Reported by W. L. Rippie September 19, 1957

INTRODUCTION

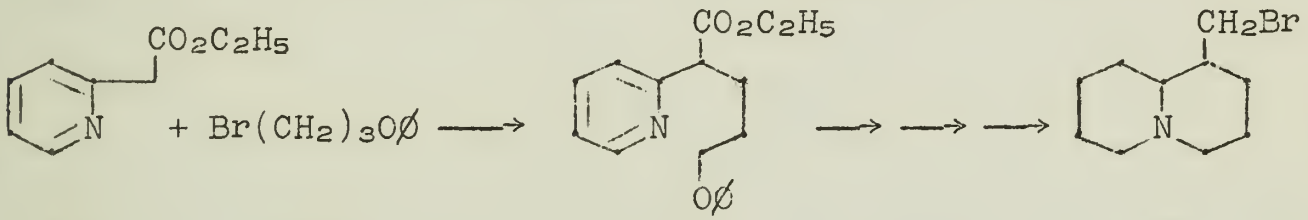
The Lupin alkaloids possess the skeletal moiety of a modified quinolizidine ring (I). The degradative structural determination and related stereochemistry of these alkaloids have been the subject of earlier review articles (1-3). Although the oxygen-free bases have been available, only in recent times have the naturally occurring oxygenated bases been obtained synthetically. The syntheses will be considered in order of increasing complexity.



I

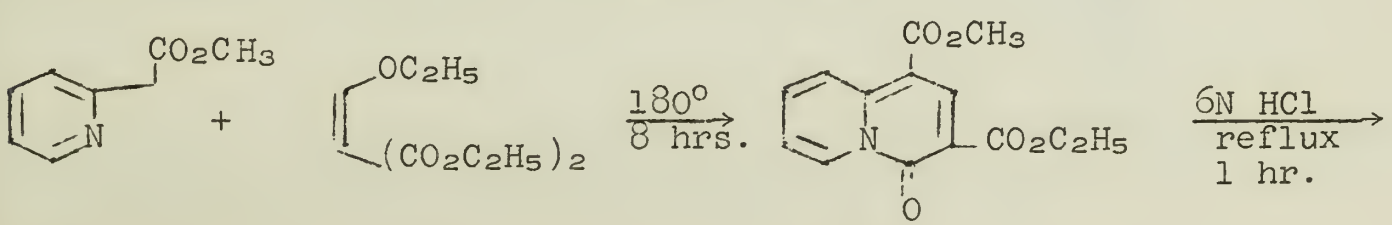
LUPINE

Ethyl 2-pyridylacetate (II) was condensed with γ-phenoxy-n-propylbromide (III) which formed ethyl δ-phenoxy-α-2-pyridyl-n-valerate (IV). Reduction of the pyridine ring in acidic medium with Adams catalyst followed by a Bouveault-Blanc reduction produced δ-phenoxy-β-2-piperidyl-n-amyl alcohol which, when refluxed in aqueous hydrobromic acid, underwent phenoxide cleavage, dibromide formation and cyclization to 1-bromomethyloctahydropyridocoline (V). Hydroxysis in refluxing aqueous sodium acetate produced (±)-lupinine (4).

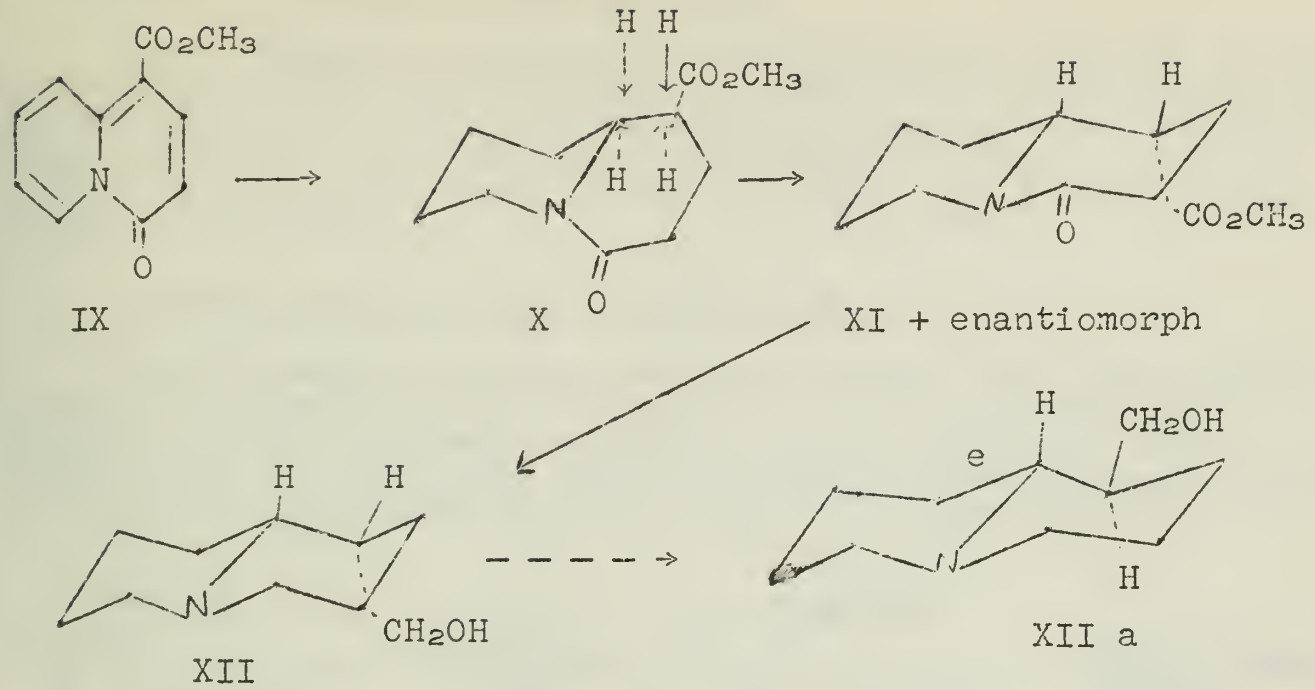


II III IV V

Boekelheide (5) synthesized (±)-lupinine (XII) from methyl 2-pyridylacetate (VI) and ethoxymethylenemalonic ester (VII). 1-Carbomethoxy-4-quinolizone (IX) was hydrogenated in acid using Adams catalyst to the α-pyridone (X), which in neutral solution was reduced to 1-carbomethoxy-4-quinolizidone (XI). (One of the enantiomorphs of the predominate racemate is shown). This lactam was reduced to the tertiary amine in strong hydrochloric acid using Adams catalyst, and the ester was reduced by lithium aluminum hydride to (±)-lupinine (XII). The infrared spectrum of (-)-lupinine in dilute solution indicated an intramolecular hydrogen-bonded OH---N (6). Lupinine is the less stable of the two 1-hydroxymethyloctahydropyridocolines as it is epimerized to the 1,10-diequatorial (+)-isolupinine ((+)-epilupinine) by refluxing sodium in benzene (7).



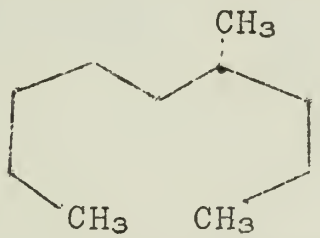
VI VII VIII



IX X XI + enantiomorph

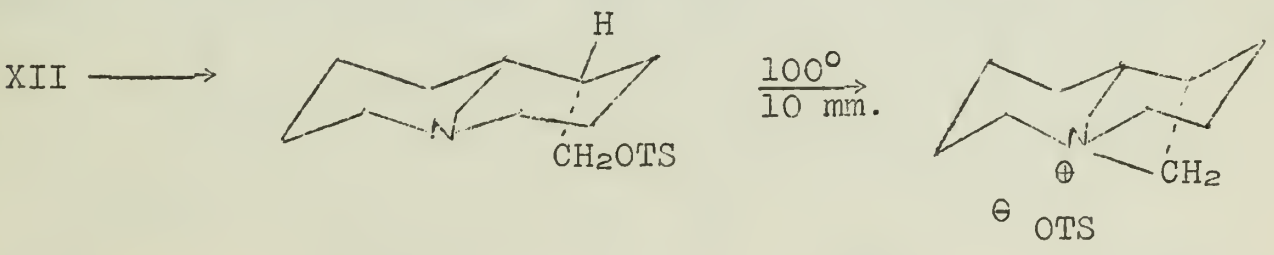
XII XII a

The absolute configurations of the asymmetric carbons in (-)-lupinine, with the C_{10}-H β and the C_1-CH_2OH α (XII) rests upon the firm basis indicated by Cookson (8) of the degradation of (-)-lupinine to (-)-4-methylnonane (XIII). (+)-Epilupinine is thus (XIIa) rather than its enantiomorph.



XIII

(±)-Epilupinine was also obtained in the earlier Clemo synthesis of (±)-lupinine (4) and has recently been synthesized by Ratusky and Sorm (9), who determined the dipole moments of the two racemates. Galinovsky and Nesvadba (10) concurred in the 1,10-cis-hydrogen relative stereochemistry for lupinine and the 1,10-trans-hydrogen for epilupinine. They found that the p-toluenesulfonic ester of (-)-lupinine rearranged to a quaternary salt, 1,5-endomethylenedecahydroquinolizidinium p-toluenesulfonate (XIV), while under the same



XIV

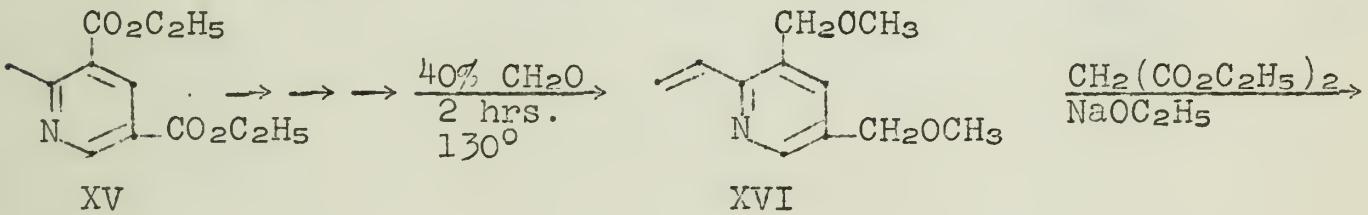
conditions (+)-epilupinine did not form a quaternary salt. Although the position isomers are not found in nature, (±)-2-, (±)-3-, and (±)-4-lupinine have also been synthesized (11, 27).

CYTISINE A TRICYCLIC LUPIN ALKALOID

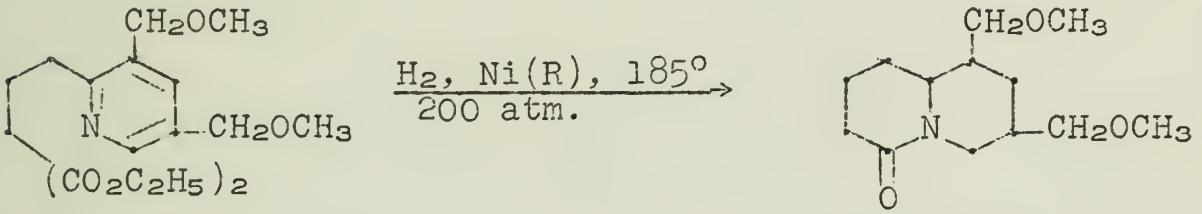
The fundamental proposition underlying the attempts to effect a synthesis of this major alkaloid of the plants of the genus Cytisus is the utilization of ring compounds possessing substituents at the positions which may later be incorporated in rings. The major difficulties are the desired stereospecific cis C ring closure and oxygen incorporation.

CLOSURE OF RINGS C AND A ABOUT RING B.

Ethyl 2-methyl-3,5-pyridinedicarboxylate (XV) was reduced by lithium aluminum hydride to the glycol which was transformed to the diether by the Williamson synthesis (12). A Michael addition to the substituted vinylpyridine (XVI) followed by reductive cyclization produced 7,9-bis-(methoxymethyl)-4-quinolizidone (XVIII)(14).

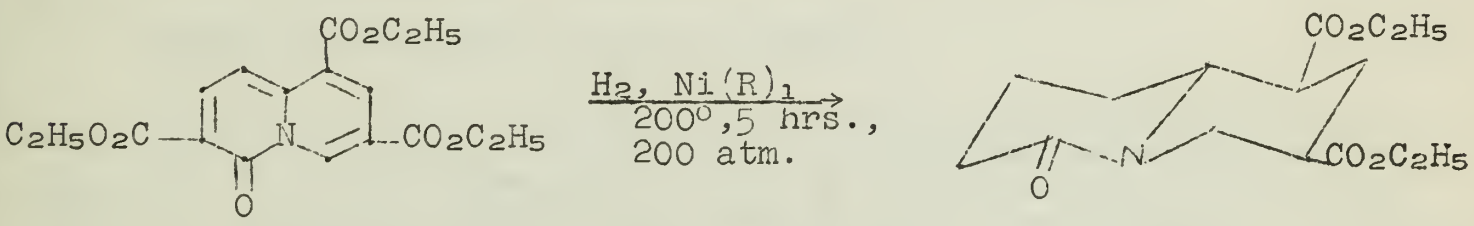


XV XVI

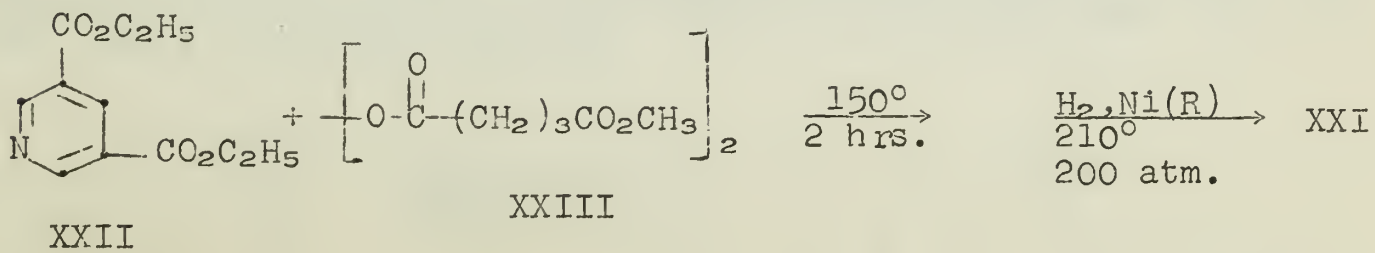


XVII XVIII

Ring A (XX) also may be constructed from (VII) and (XV). Goldschmidt and Munsinger (13) established that acyl peroxides attack simple pyridines at the 2- and 4-position. Similarly the peroxide of glutaric acid half ester (XXIII) attacked 3,5-dicarbethoxypyridine at the 2-position (14). The product of the peracid attack on (XXII) was reductively cyclized to 7,9-dicarbethoxy-4-quinolizidone (XXI) (preferred conformation of 7,9-cis will be diequatorial).

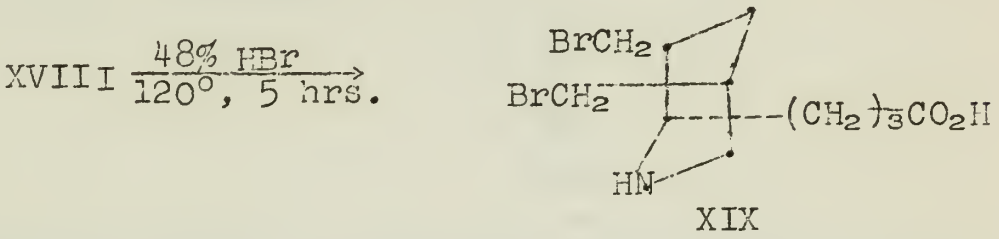


XX XXI

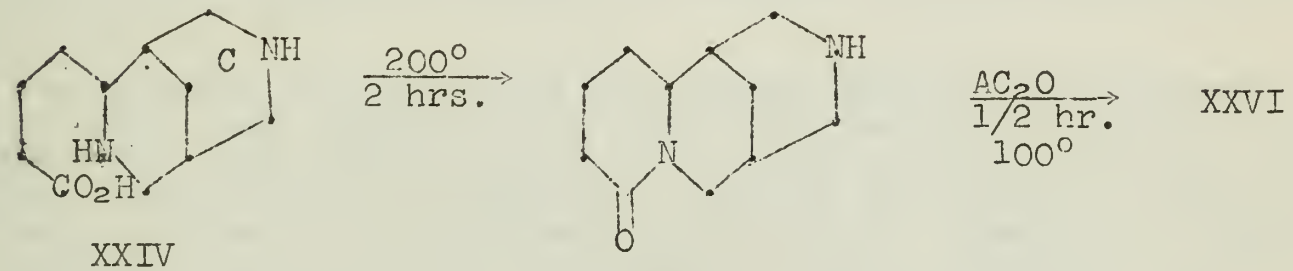


XXII XXIII

To allow greater conformational flexibility for the closure of ring C, ring A (XVIII) was opened by hydrolysis with hydrogen bromide, which cleaved the ether and formed the bis-bromomethyl compound (XIX). This with alcoholic ammonia closed ring C (XXIV). Heating the amino acid (XXIV) in methylnaphthalene furnished the lactam, tetrahydrocytisine, as a mixture of racemates.

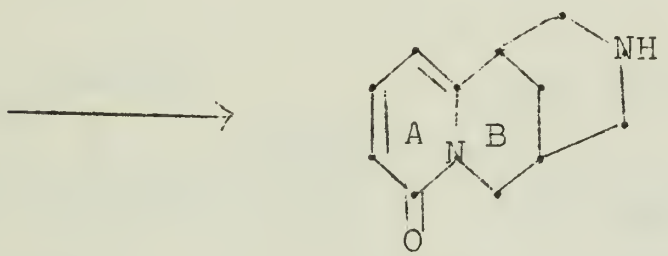


XIX



XXIV

XXV

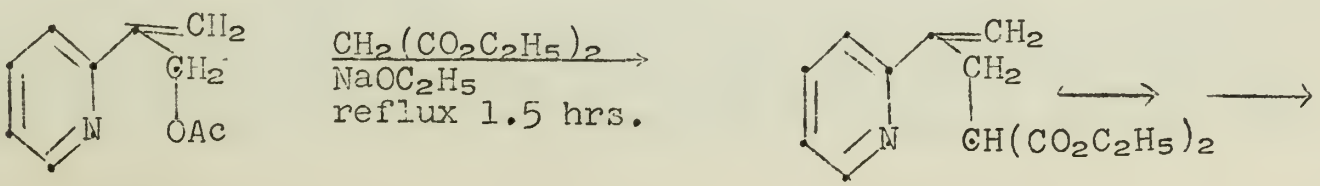


XXVII

Tetrahydrocytisine (XXV) was acetylated (XXVI) and subsequently dehydrogenated (15) by heating with 10% palladium-on-carbon for 3.5 hours at 260°. Some deacetylation (ca. 70%) accompanied the dehydrogenation to (±)-cytisine (XXVII).

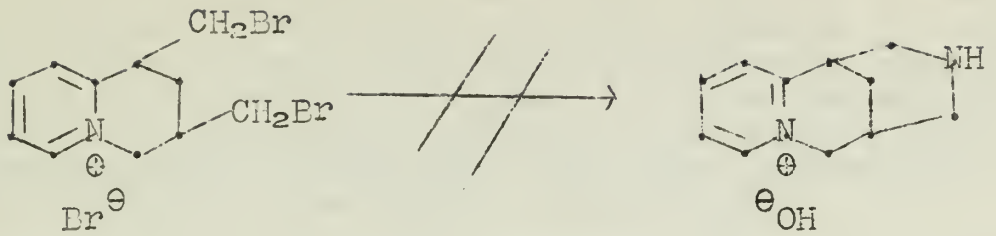
FORMATION OF RINGS C AND B ON RING A

Bohlmann, Ottawa and Keller (16) caused 40% formaldehyde to react with α-picoline at 130° to form α-dimethylolpicoline, which was acetylated and dehydrated to the β-acetoxymethylvinylpyridine (XXVIII). A Michael condensation formed ethyl α-carbethoxy-γ-methylene-γ-2-pyridylbutyrate (XXIX). Lithium aluminum hydride reduction produced the diol which was treated with hydrobromic acid and red phosphorus for 4 hours at 150°. The resulting dibromide (XXX) did not form a C ring with ammonia.



XXVIII

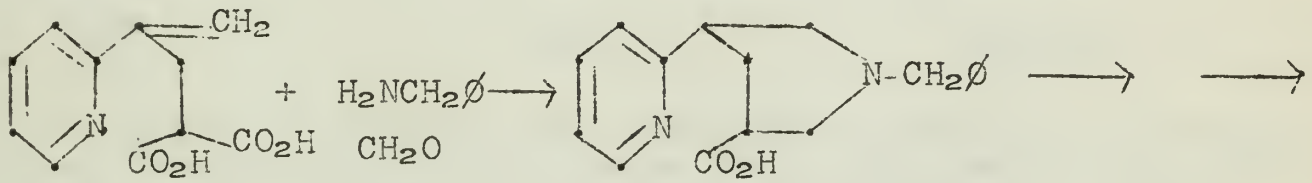
XXIX



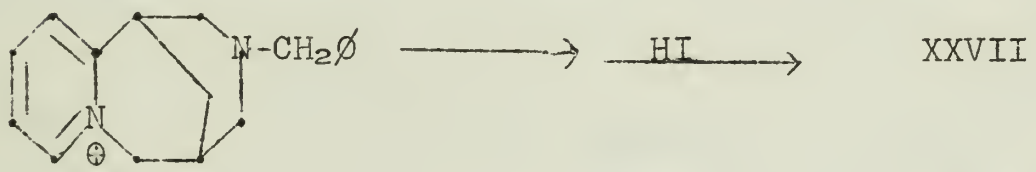
XXX XXXI

The addition of hydrogen bromide is analogous to its reaction with 2-vinylpyridine (17).

van Tamelen (18) converted the diester (XXIX) to 2-(α-pyridyl)-allylmalonic acid, (XXXII), which was condensed with benzylamine and formaldehyde. Esterification of the resulting XXXIII, followed by a lithium aluminum hydride reduction, produced the methylol compound. This was refluxed with hydrobromic acid, and the bromomethyl compound was cyclized to the tricyclic pyridinium bromide (XXXIV). Alkaline ferricyanide oxidation (19) and N-benzyl cleavage produced (±)-cytisine.



XXXII XXXIII



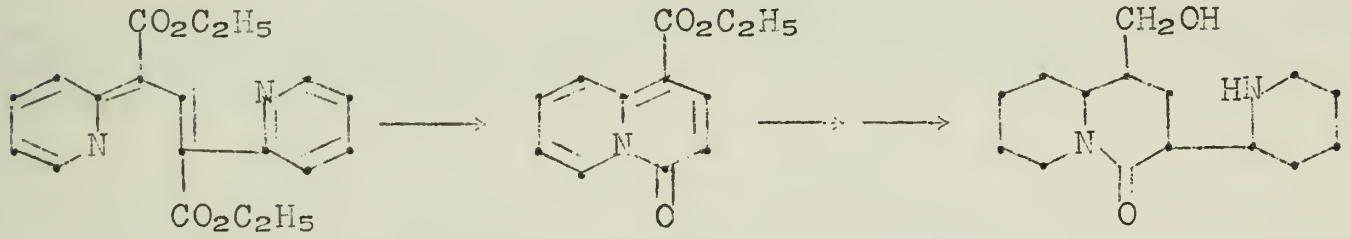
XXXIV

Alternatively, the above methylol may be synthesized from the condensation of α-pyridylacetamide and ethyl methylenemalonate to 3-(α-pyridyl)-5-carboethoxyglutarimide followed by benzylation and lithium aluminum hydride reduction (20).

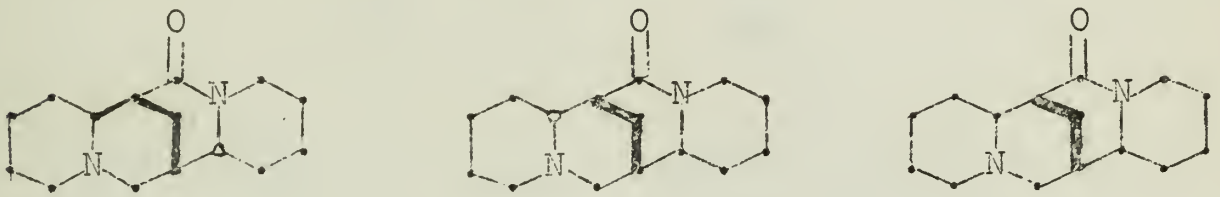
TETRACYCLIC LUPIN ALKALOIDS

(±)-Aphyllin (XXXV) and its (racemic) stereoisomers, oxosparteine (XXXVI) and desoxylupanoline (XXXVII), have been obtained from the cyclization of the stereoisomers of 1-carboxy-4-keto-3-(2'-piperidyl) octahydropyridocoline which was originally synthesized by Clemo (21)

from ethyl 2-pyridylacetate and ethyl orthoformate. Ring closure of the intermediate bis-methenyl compound (XXXVIII) to 1-carbethoxy-4-keto-3-(2'-pyridyl)pyridocoline (XXXIX) occurred in refluxing acetic anhydride. The aromatic rings were reduced with hydrogen and Adams catalyst in acetic acid at 130 atm. and room temperature. From the Bouveault-Blanc reduction of (XXXIX), four racemic alcohols (XL) were isolated by chromatography, and these oxidized by chromic acid and then cyclized to the desired lactams (22).

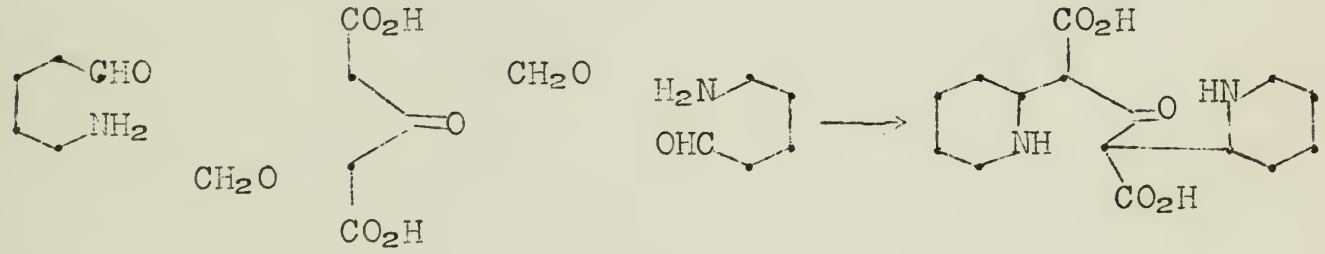


XXXVIII XXXIX XL

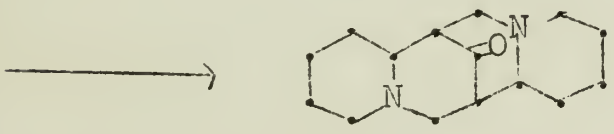


XXXV XXXVI XXXVII

Anet, Hughes and Ritchie (23) hydrolyzed 5-amino-1,1-dicarboxypentane and coupled the aldehyde-amine (XLI) with acetonedicarboxylic acid at pH 13 for 3 days. To the postulated intermediate 1,3-bis-(2'-piperidyl)propanone (XLII), formaldehyde was added, the pH was adjusted to 3, and after 3 days spartein-8-one (XLIII) was isolated in 30% yield.



XLI XLII

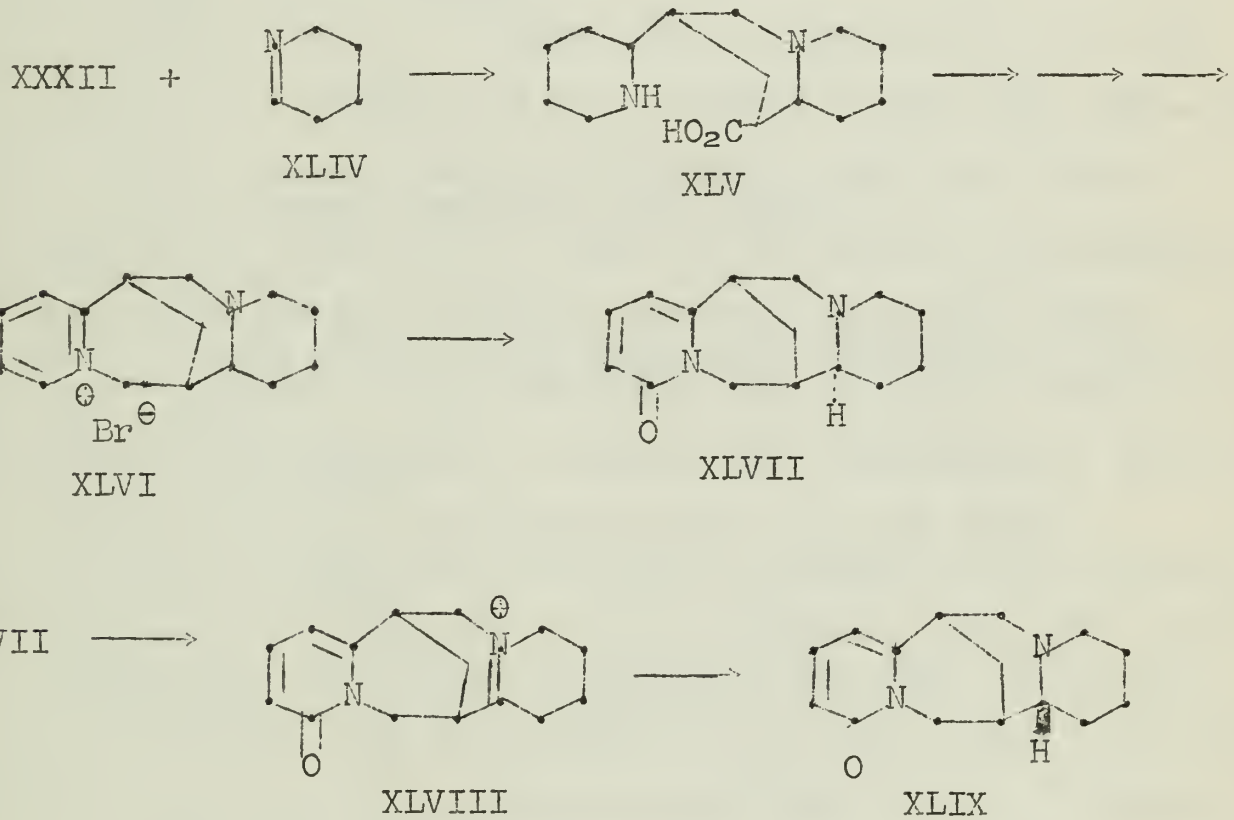


XLIII

The unsymmetrical, partially aromatic, bridged tetracyclic lupin alkaloid anagyrine has been synthesized by van Tamelen (24). As a product of bleaching-powder on piperidine acetate, Schöpf (25)

obtained 1-chloropiperidine which trimerized to α-tripiperideine. This trimer depolymerized to Δ^4-piperideine (XLIV) which reacted with 2-(α-pyridyl)-allylmalonic acid (XXXII) to form 3-(α-pyridyl)-quinolizidine-1-carboxylic acid XLV). A sequence of esterification, lithium aluminum hydride reduction and bromination produced the tetracyclic pyridinium base (XLVI) which when oxidized by alkaline ferricyanide formed (±)-anagyrine (XLVII).

A mercuric acetate oxidation of (XLVII) to the ternary iminium salt (XLVIII) followed by catalytic hydrogenation with 6% palladium-on-strontium carbonate produced the diastereoisomeric racemate, (±)-thermopsine (XLIX) (26).



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THE STRUCTURE OF LABDANOLIC ACID AND CATIVIC ACID-TWO NEW BICYCLIC DITERPENES

Reported by K. D. Berlin September 23, 1957

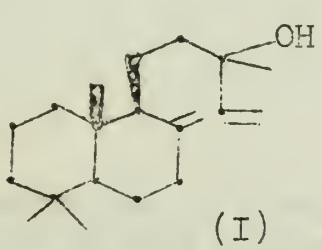
INTRODUCTION

From the bramble of Cistus Landiferus a resin is extracted by boiling the wood in water (1, 2). Only 1-2% of volatile oil can be removed from this gum or resin by steam distillation. Labdanolic acid, a new bicyclic diterpene, has been isolated from the oil, and its structure and most of its stereochemistry have been elucidated.

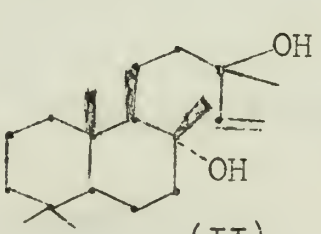
SEPARATION AND CHARACTERIZATION

The acidic portion of an ether extract of the resin was esterified and the resulting mixture chromatographed (2). The elution of the third fraction, which was about 25% of the oil by weight, yielded a new hydroxy acid whose equivalent weight determination confirmed the formula $C_{20}H_{36}O_3$. From the infrared spectrum which indicates the absence of a double bond and from the equivalent weight determination, it seemed to the investigators that the new compound might be a saturated bicyclic diterpenic acid. The infrared spectrum of the methyl ester displays bands at 1738 $cm.^{-1}$ (ester) and 3560 $cm.^{-1}$ (hydroxyl). As the hydrolysis of the ester could be effected easily with sodium and alcohol, it was reasoned that the compound, in contrast to the majority of diterpene acids, probably did not possess a carboxyl group in the 4-position. Since the acid was unfavorable for handling, the remainder of the work was performed chiefly on the methyl ester (1, 2).

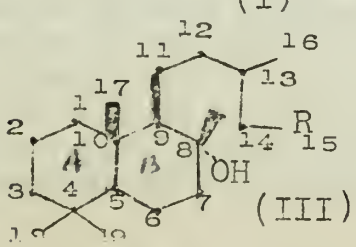
The hydroxyl group was acetylated only under drastic conditions, and, in fact, some dehydration product (V) occurred (1). This compound (V) proved to be identical with the olefin obtained by treating the ester with phosphoryl chloride in pyridine. The unsaturated alcohol (VI) obtained by reduction of (V) with lithium aluminum hydride, gave 1,2,5-trimethylnaphthalene and 1,2,5,6-tetramethylnaphthalene when heated with the platinum-charcoal catalyst. The latter two compounds were characterized by their previously noted ultraviolet spectra (3) and their 1,3,5-trinitrobenzene adducts (3, 4). The isolation of these two compounds suggested that this new acid was related to a group of bicyclic diterpenes, examples of which are manoöl (I) and sclareol (II) (5-8). Thus a general structure was proposed as a working model, (III) (or (IV)) (2).



(I)

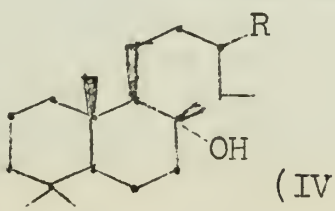


(II)

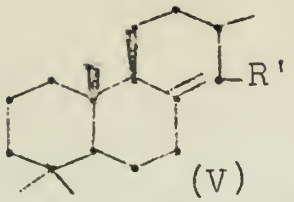


(III)

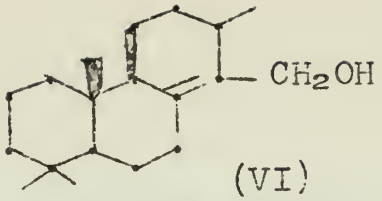
$R = CO_2H$



(IV)

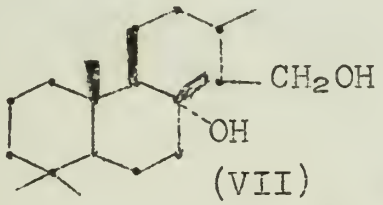


(V) R=CO_2H (or CO_2Me)

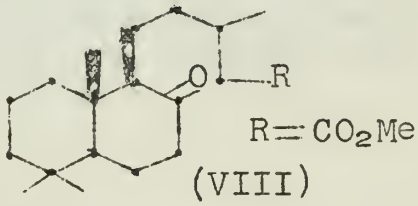


(VI)

As further evidence for a tertiary hydroxyl group in the molecule, mild chromic acid oxidation of the ester gave back only starting material while lithium aluminum hydride reduction gave a diol (VII) which could form only a monoacetate readily. The infrared spectrum of (V) indicates a vinylidene structure (890 $cm.^{-1}$ and 1645 $cm.^{-1}$) which was verified by ozonolysis; formaldehyde and a keto ester (VIII) were obtained. The investigators state that these



(VII)

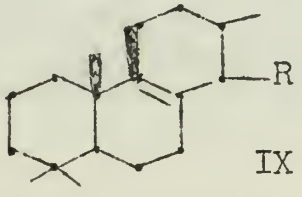


(VIII)

results indicate that methyl labdanolate probably contains an 8-hydroxyl in the equatorial conformation (α-on the ring) to account for the formation of an exocyclic rather than endocyclic double bond on dehydration (2). This type of dehydration was observed previously in studies on 3-methyl cholestanols with similar results being obtained (9). The production of the methylene compound (V) can be rationalized by the fact that the equatorial hydroxyl group can become staggered only with respect to a 8-methyl hydrogen atom. A C_8 axial hydroxyl group could be staggered with respect to αC_7-H, C_7, and C_8, and the normal trans elimination to give the trisubstituted or tetrasubstituted endocyclic double bond would be expected.

The keto ester (VIII) produced by ozonolysis of the unsaturated ester (V), formed an oxime but no 2,4-dinitrophenylhydrazone. These data plus the infrared absorption at 1712 $cm.^{-1}$ suggested that the carbonyl group might be slightly hindered and possibly situated in a ring system as was depicted in (VIII).

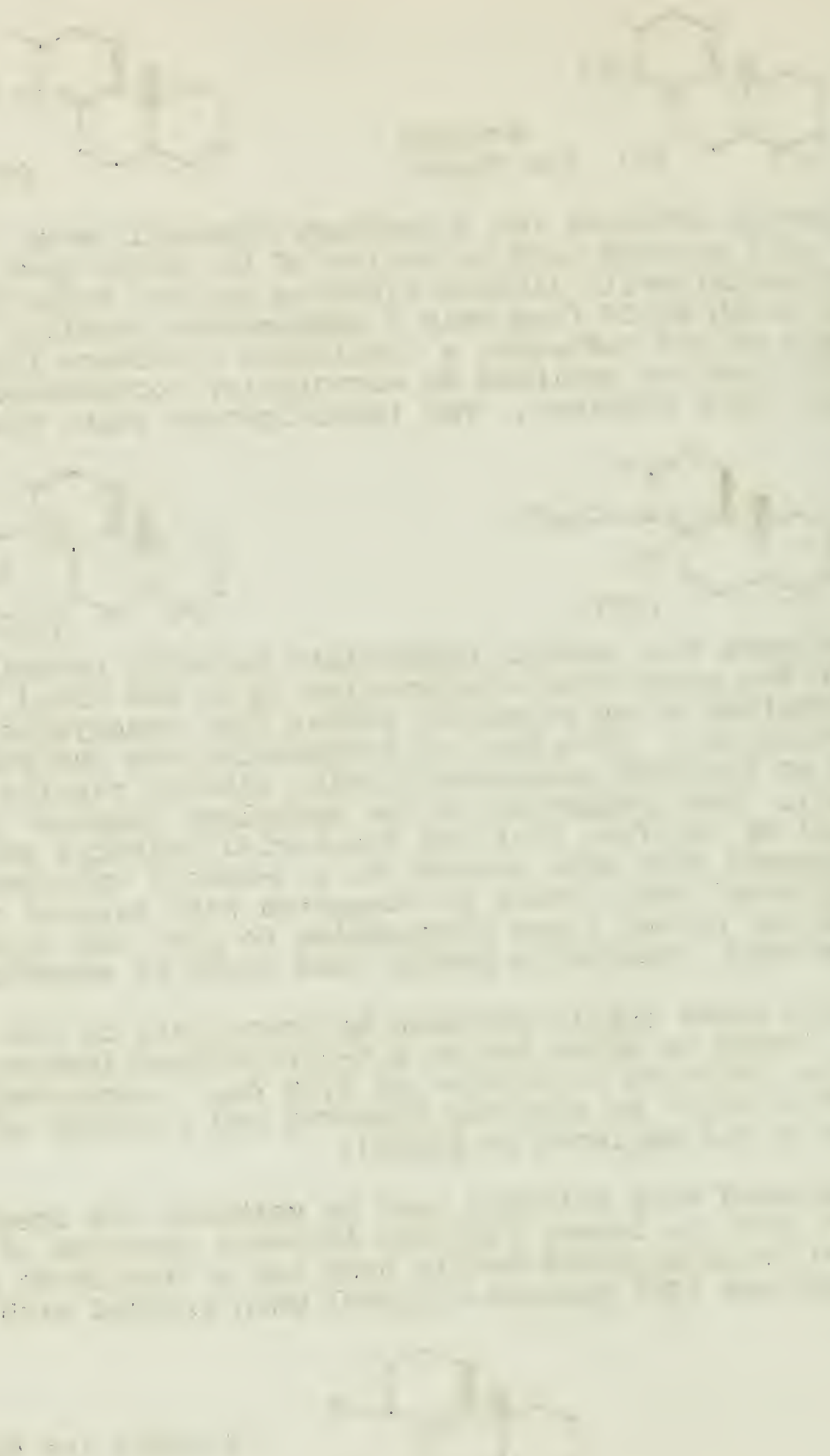
When treated with sulfuric acid in methanol the unsaturated ester of (V) gave an isomer (IX) the infrared spectrum of which indicates no trisubstituted double bond nor a vinylidene group (2). This new compound (IX) yielded a glycol when treated with

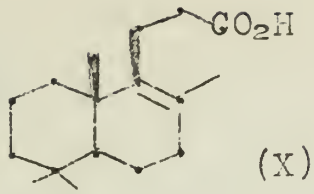


IX

R=CO_2H (or CO_2Me)

osmium tetroxide in pyridine. Thus it was suggested that a tetrasubstituted double bond might be present and that if the stereochemistry was the same as in manoöl (I) the addition would have likely taken place on the unhindered (α) side of the molecule. A literature survey uncovered a similar situation in which (X) was thought to give β-addition in the same hydroxylation reaction (10). Hydrogenation of (IX) with the Adams catalyst gave only one isomer.

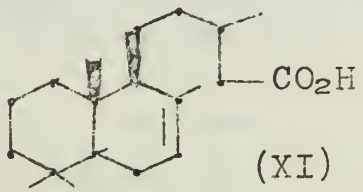




(X)

It was observed, however, that a change in molecular rotation (Δ M= - 112) for this reaction was very similar to that (Δ M= - 136) found when (X) was hydrogenated (10, 12). When (V) was hydrogenated two products were obtained; one was a solid and the other an oil. The solid isomer was identical with the compound obtained by hydrogenation of the acid isomerized ester (IX). Thus no skeletal rearrangement had occurred during the acid isomerization.

The literature revealed that the dihydro derivative of cativic acid (XI) might be similar in nature to one of the hydrogenation products of (V) (11). Methyl dihydrocativate was, indeed, identical

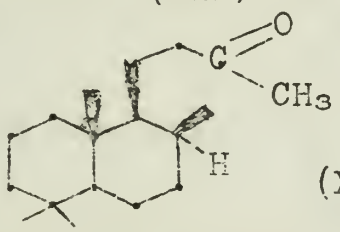


(XI)

with the solid hydrogenated compound obtained from (V) and from (IX) (the proof of structure for cativic acid is given later). With this evidence at hand the acid (III) was degraded to compounds whose structures and stereochemistry were definitely known.

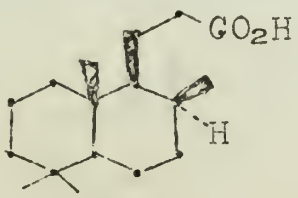
PROOF OF STRUCTURE; STEREOCHEMISTRY

Proof that (III) and not (IV) was the correct structure of labdanolic acid was accomplished by employing the Barbier-Wieland technique on the solid hydrogenation product obtained from the ester of (V) (2). The resulting ketone (XII) was oxidized in a haloform

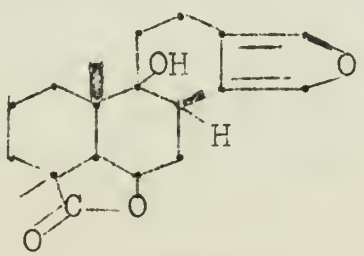


(XII)

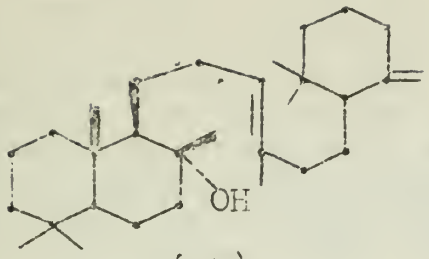
reaction to the corresponding acid (XIII). This acid was shown to be identical with an acid obtained from marrubin (XIV) and which had been shown (12) to be identical with an acid obtained from ambrein (XV) (13). The acid (XIII) obtained from labdanolic acid (III), proves the rings A-B are trans-fused and the absolute configuration at C_{10} is the same as in ambrein and in the di- and triterpenes (2).



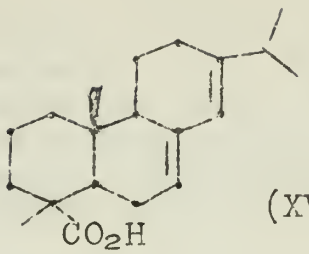
(XIII)



(XIV)

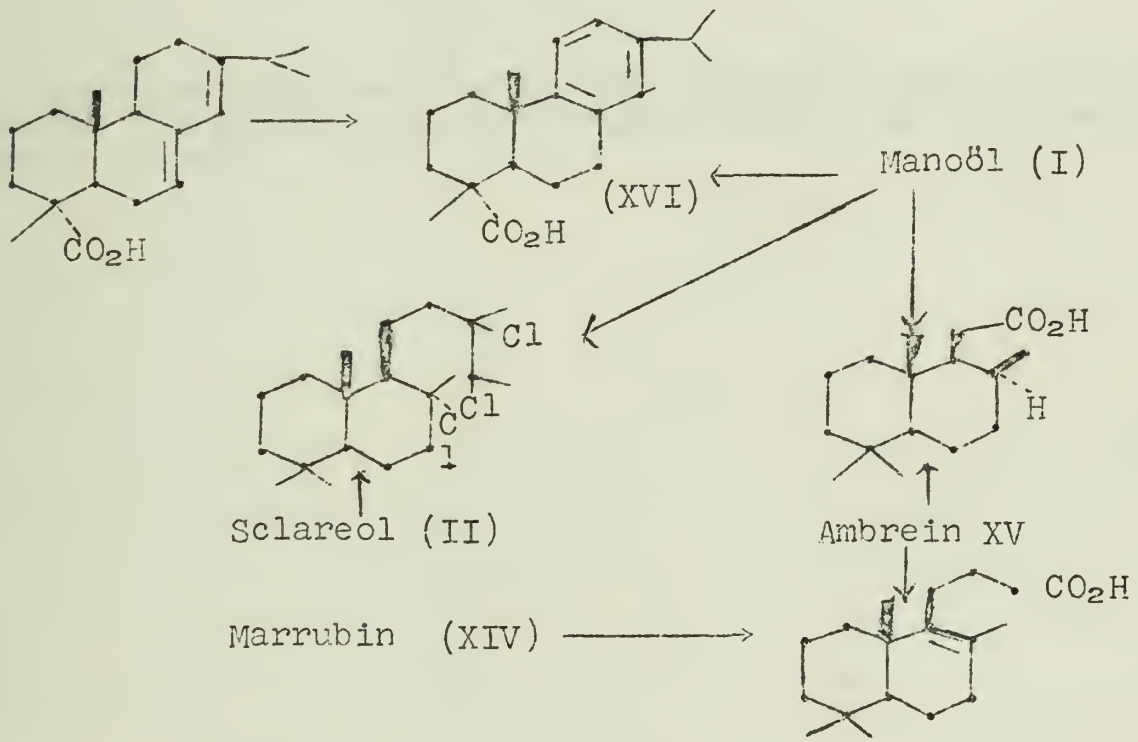


(XV)

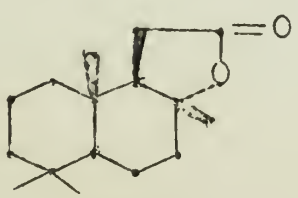


(XVI)

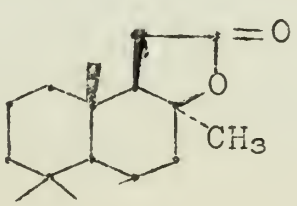
This is better understood by examining the relationship of manoöl (I), sclareol (II), marrubin (XIV), and ambrein (XV) to abietic acid (XVI) whose carbon skeleton and configurational assignments will be assumed as shown and will not be discussed; some references are cited (14-19). The following brief reaction scheme demonstrates the relationship of (I), (II), (XIV), (XV), and (XVI) which is given in some excellent reviews (5-7, 10, 12, 17, 19). As the A-B ring junction is trans-fused in abietic acid it is also trans-fused in the compounds cited and in labdanolic acid.



Concerning the orientation of the side chain at C_9 and the hydroxyl group at C_8, previously established as α-oriented, one needs only to examine the literature on the degradative studies of sclareol (II) and ambrein (XV) (7, 8, 20, 21). Both of these compounds are converted to a lactone (XVII) which has been further studied by many (22-25). They have found that this compound (XVII)



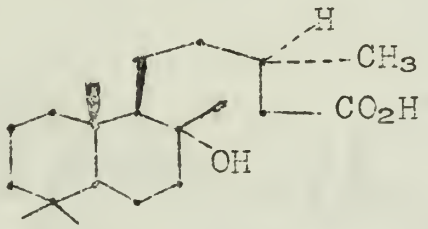
(XVII)



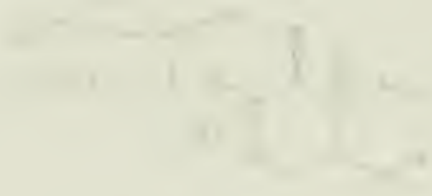
(XVIII)

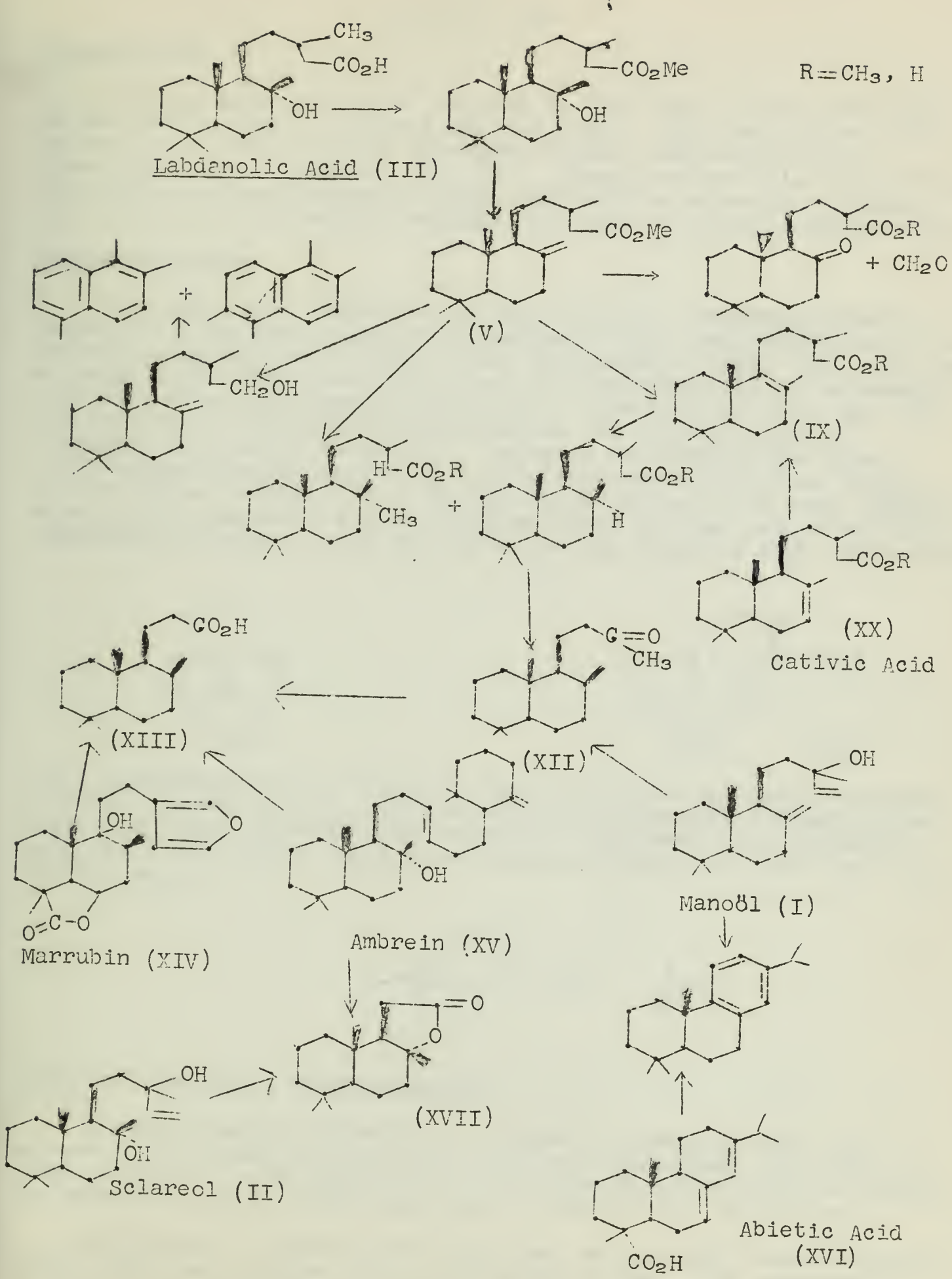
can be isomerized to the cis isomer (XVIII). If the C_9 side chain was α-oriented in (XVII) the isomerization would lead to a trans-isomer of the diaxial conformation which would be highly strained. Thus the β-oriented C_9 side chain theory seems secure. Supporting evidence for the existence of identically situated hydroxyl groups in sclareol and labdanolic acid was found by comparing the molecular rotation differences between sclareol (II) and manoöl (I) ($\triangle M = + 98°$) and between labdanolic acid (III) and its dehyration product (V) ($\triangle M = + 99°$) (2).

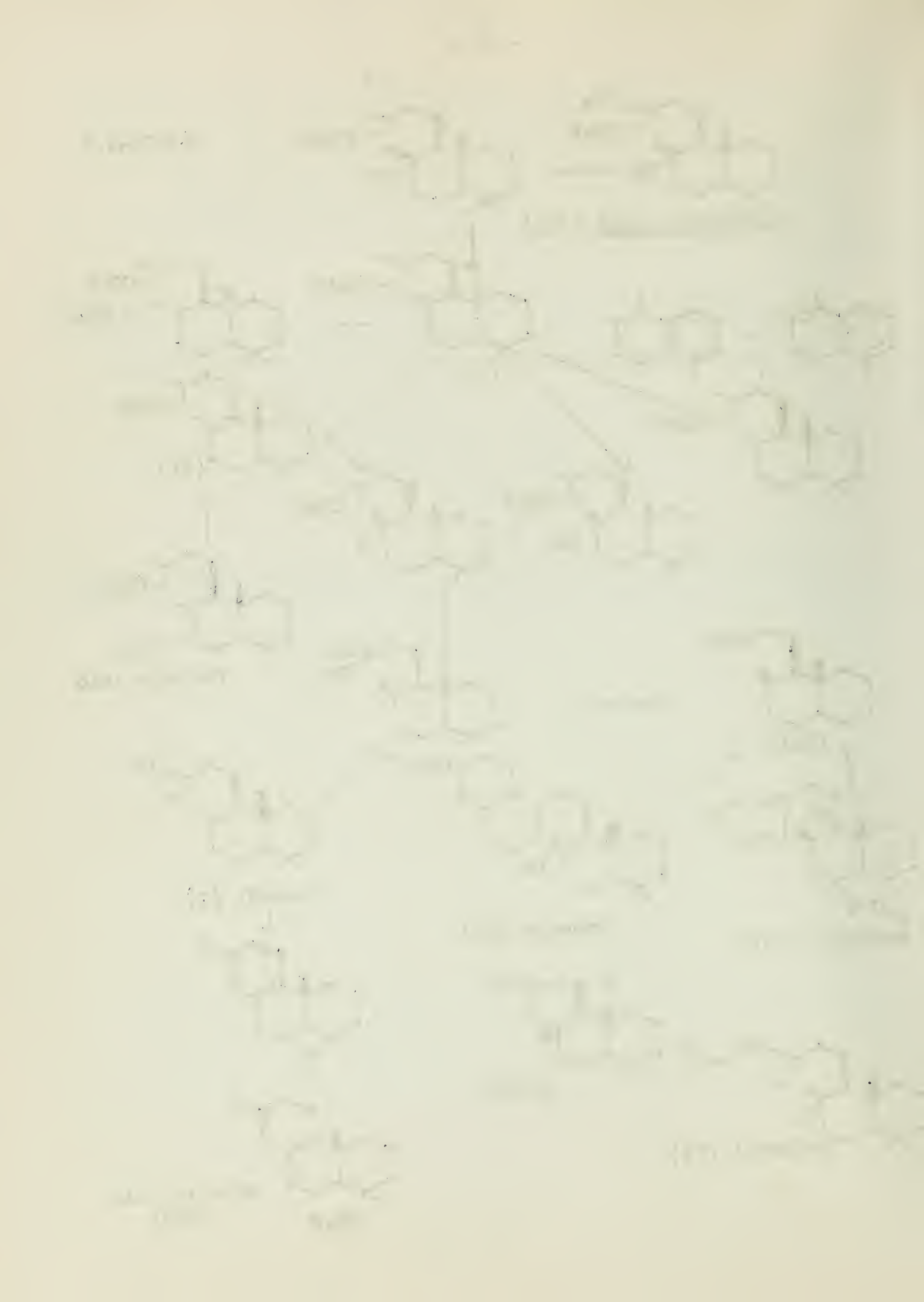
The remaining stereochemical assignment to be made in labdanolic acid is at position 13. The investigators who have contributed most to the elucidation of this natural product, have reported that this problem is being studied and results should be forthcoming.



A general outline showing the principal reactions and compounds involved in establishing the structure assigned to labdanolic acid is given below.




R = CH3, H
Labdanolic Acid (III)
(V)
(IX)
(XX)
Cativic Acid
(XII)
(XIII)
Marrubin (XIV)
Ambrein (XV)
Manoöl (I)
(XVII)
Sclareol (II)
Abietic Acid
(XVI)



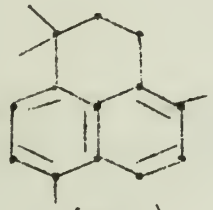
CATIVIC ACID

INTRODUCTION

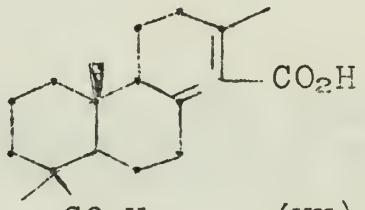
Cativic acid was first isolated in 1938 from cativo gum found in the cativa tree of Central America (26). Only recently was its membership in the bicyclic diterpene family confirmed and its stereochemistry elucidated (11, 27). Since cativic acid (XI) differs in structure from labdanolic acid (III) by one molecule of water, the similarity in chemical methods used here is quite understandable.

CHARACTERIZATION

The acid [(α) -6.54°] is separated from a petroleum ether fraction of the cativo gum by formation of its cyclohexylamine salt and then regenerated by very dilute hydrochloric acid. The acid can be esterified readily and was shown to be unsaturated by perbenzoic acid titration and bromine absorption. With this evidence and the neutralization equivalent determination the formula $C_{20}H_{34}O_2$ suggested a bicyclic diterpene. Selenium dehydrogenation gave 1,2,5-trimethylnaphthalene and 1,1,4,7-tetramethylphenalan (XIX). As the latter contains 17 of the 20 carbon atoms it is very significant. This compound is also obtained under similar conditions from agathenedicarboxylic acid (XX) (28) and has recently been synthesized

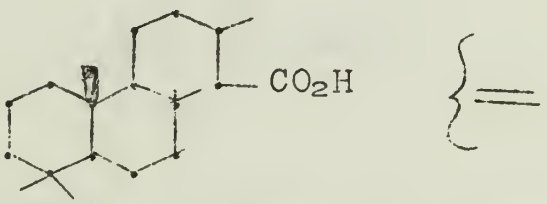


(XIX)



(XX)

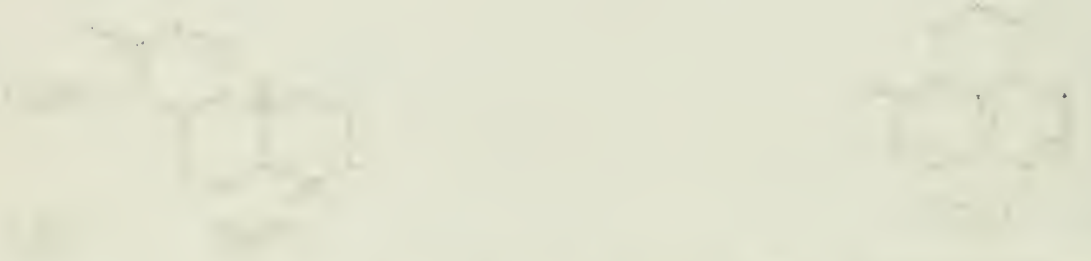
(29). Dehydrogenation of cativic acid (XI) with palladium-charcoal catalyst yielded another hydrocarbon 1,2,5,6-tetramethylnaphthalene which was identical with that previously obtained from labdanolic acid (2). From these facts a provisional formula was put forth for cativic acid.



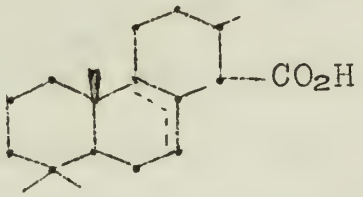
PROOF OF STRUCTURE; STEREOCHEMISTRY

Barbier-Wieland degradation of methyl dihydrocativate gave a ketone (XII) identical with that obtained from manoöl (I) (30) and from labdanolic acid (III) (2). Thus dihydrocativic acid is related in structure and in stereochemistry to the di- and triterpenes.

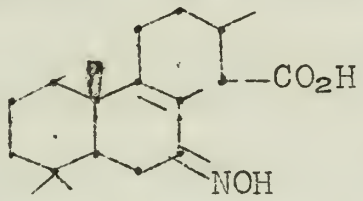
Ozonolysis of cativic acid produced no cleavage fragments, which would indicate a double bond in the ring system. The ozonolysis product was crystalline and gave a positive iodoform test which



indicates the double bond may terminate at a tertiary carbon to which a methyl group is attached. The tentative structure is shown below:



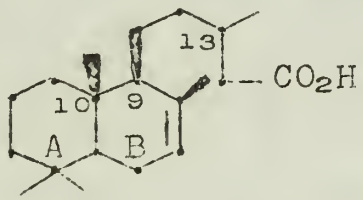
The reaction of nitrosyl chloride in chloroform upon methyl cativate results in the formation of an α,β-unsaturated oxime (XXI), which places the unsaturation at the 7-8 position in cativic acid. The nitrosyl chloride adduct which is the intermediate in this reaction, undergoes elimination of hydrogen chloride spontaneously, followed



(XXI)

by enolization. Several other examples analogous to this reaction are also known (30, 31). As the ozonolysis product gives a positive Tollens test for an aldehyde structure, the 7-8 position of unsaturation is confirmed.

The relationship of cativic acid to manoöl and labdanolic acid thus allows the stereochemical assignments to be made at positions 9 and 10 which are β-oriented as shown, and the A-B ring junction as trans-fused. Thus again as in labdanolic acid the stereo



assignment for the methyl group at carbon 13 is lacking and evidence should be forthcoming in the near future to clear up this matter.

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GEMINATE RECOMBINATION OF FREE RADICALS IN SOLUTION

Reported by D. E. McGreer September 26, 1957

INTRODUCTION

Free radicals are often obtained by the homolytic cleavage of molecules through thermal or photochemical dissociations.

$$AB + h\nu (\text{or } \triangle H) \longrightarrow A\cdot + B\cdot$$

In solution it is found that not all the radicals formed are available for reactions such as polymer initiation or other forward reactions due to the occurrence of the reverse reaction.

$$A\cdot + B\cdot \longrightarrow AB$$

This seminar will discuss this recombination reaction and will suggest some instances where such a reaction may play an important role.

THEORY

There are many paths by which radical fragments may react. These are:

1. Primary Recombination or "Cage Effect",- The radical fragments may loose their energy quickly by collision with solvent molecules. If the fragments do not become separated by more than one molecular distance (ie. are held in a solvent cage) then they may recombine. Cage recombination must occur before either particle undergoes a diffusive displacement. The average time between diffusive displacements for particles in solution is about 10^{-11} seconds (1).

2. Secondary Recombination,- The radical fragments may escape from the solvent cage but under random diffusion return to recombine with their original partners. The probability β that two fragments will undergo at least one encounter after initial separation by diffusion depends on the length of the displacements and the encounter diameter (2). If the ratio of these two distances is one then the probability β is .53. In free radical recombination reactions the energy of activation is low and the probability that two fragments will react during an encounter approaches one. We may thus expect secondary recombination to involve approximately half of the radicals formed. If, however, the original separation of the particles is several molecular distances β is reduced and the amount of secondary recombination is reduced.

Diffusion kinetics (2,3) of this type are based on time dependent probabilities. It is calculated that after 10^{-9} seconds the original fragments will have separated to such an extent that the probability of recombination will be negligible.

The above processes of recombination are termed "geminate recombination" (1). Often the term "cage effect" has been used to mean geminate recombination.

3. Combination of Fragments from Different Dissociations,- The fragments surviving recombination enter a steady state from which they may

react with other species in the solution by regular kinetics. One such reaction is with fragments from other dissociations.

4. Reaction with Scavengers,- The steady state concentration for free radicals is estimated to be 10^{-8} mole/liter. If the rate of reaction between scavengers and radicals is of the same order as the rate for radicals with radicals a scavenger concentration of 10^{-3} mole/liter will be sufficient to react with all radicals surviving geminate recombination. At higher concentrations of scavenger the probability that fragments from a dissociation will encounter a scavenger molecule in less than 10^{-9} seconds will be sufficiently high that competition between the scavenger reaction and secondary recombination can occur. A theory for such competing reactions has been developed by Hamill (3) and some experiments illustrating this theory are given below.

5. Induced Reactions,- In considering the fate of radicals, one must include the possibility that induced reactions of the following nature may occur.

$$RCO_2\cdot + RC(=O)-O-O-C(=O)-R \longrightarrow RCO_2R + RCO_2\cdot + CO_2$$

Such a reaction could be confused with a dissociation recombination.

$$R-C(=O)-O-O-C(=O)-R \longrightarrow [2R\,C(=O)-O\cdot] \longrightarrow [R\,CO\cdot + R\cdot + CO_2] \longrightarrow R\,C(=O)-OR + CO_2$$

The rate of the induced reaction should depend on the peroxide concentration while that of the recombination reaction should not. This can be used to distinguish the two reactions.

6. Concerted Reactions,- It is often possible that the product believed to be obtained by radical recombination is really obtained through a concerted reaction. An example of such a situation would be

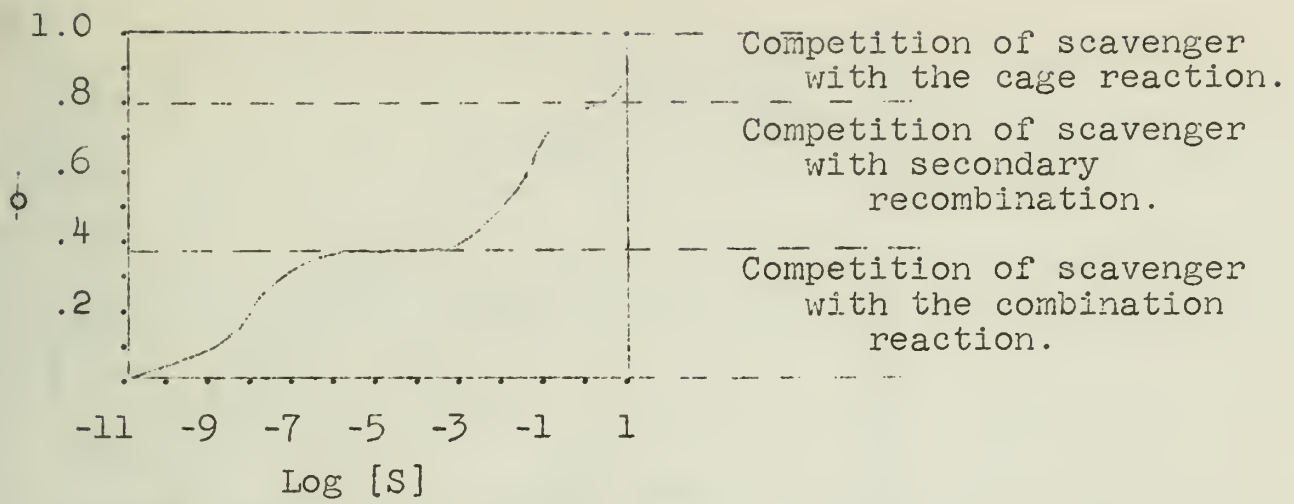
$$R-N=N-R \longrightarrow [R\cdot + R\cdot + N_2] \longrightarrow R-R$$

$$R-N=N-R \longrightarrow \left[R \cdots R \;\; N=N\right] \longrightarrow R-R + N_2$$

7. No Reaction,- In photochemical reactions a molecule may absorb light energy but be deactivated before dissociation. This also may be confused with recombination.

Noyes (1) has calculated for a hypothetical case the effect of scavenger concentration on the quantum yield ϕ of the scavenger reaction assuming that all the light energy absorbed causes dissociation. The results of this calculation are shown in Fig. I.

Fig. I



[S] Conc. of Scavenger

EXPERIMENTAL

PHOTOCHEMICAL DISSOCIATION OF TRIIODIDE ION

Hamill (29) has demonstrated the competition of a scavenger reaction and a secondary recombination reaction. He has studied the photochemical dissociation of triiodide ion at 436 and 365 mμ. in the presence of manganous ions.

$$I_3^- + h\nu \longrightarrow I_2^- + I\cdot$$

$$I\cdot + MnII \longrightarrow I^- + MnIII$$

$$I\cdot + I_2^- \longrightarrow I_3^-$$

Manganous ions are efficient scavengers for iodine radicals and at a concentration of 10^{-3} mole/liter effectively remove all iodine radicals escaping recombination. It was found that the quantum yield ϕ (based on the yield of MnIII and the light absorbed) is independent of light intensity, Mn(II) concentration and iodine concentration but it is dependent on wave length, temperature and iodide concentration.

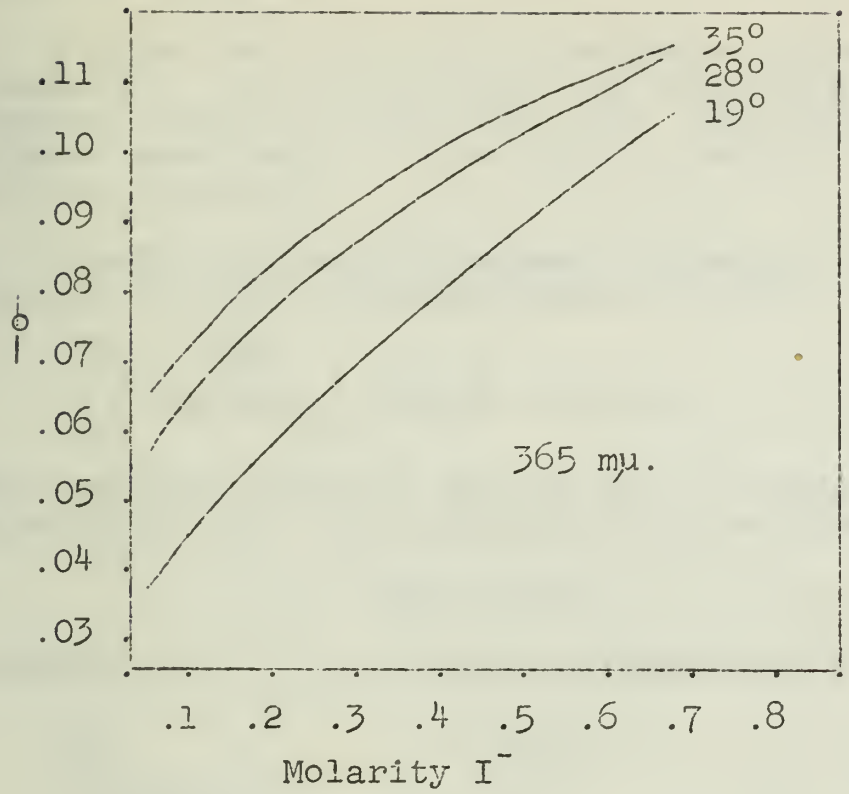
The iodide is believed to increase the efficiency of the scavenger reaction. Recombination of two diiodide radical ions is prevented by charge repulsion.

$$I\cdot + I^- \longrightarrow I_2^-$$

$$I_2^- + MnII \longrightarrow 2I^- + MnIII$$

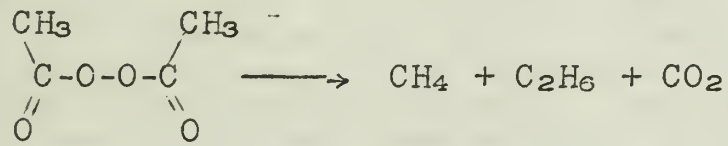
The effect of iodide concentration is shown in Fig. 2. Hamill (3) has developed a theory, based on time dependent probabilities, about the competetion of scavenger reactions and secondary recombination. This theory predicts correctly that - log ϕ is linearly proportional to $X^{1/2}$ where X is the mole fraction of scavenger.

Fig. 2



THERMAL DECOMPOSITION OF ACYL PEROXIDES

Szwarc (4.5) has studied the decomposition of acetyl peroxide both in the gas phase and in solution. In isooctane, acetyl peroxide decomposes thermally to yield methane, ethane and carbon dioxide.



In the gas phase the major product is ethane.

When a scavenger such as quinone or iodine is added to the reaction in solution the formation of methane is suppressed but the ratio of ethane to carbon dioxide is only slightly reduced. See Table I.

The ethane must be formed either by geminate recombination or by a concerted mechanism. If the ethane was formed by a concerted mechanism then such a mechanism should also be possible in the gas phase. In the gas phase, the presence of iodine completely suppresses the formation of ethane. See Table II.

Table I

Ac_2O_2-5×10^{-3}M in isooctane; t-85°C; decomposition $\sim$ 60%

mole % I_2	$2C_2H_6/CO_2$	CH_4/CO_2
0	.072	.80
.1	.062	.010
.2	.062	.001

Table II

flow system; partial pressures of Ac_2O_2 .1 mm, of toluene 15 mm

partial pressure of I_2	$2C_2H_6/CO_2$
.00	1.00
.064	.034
.12	.020
.23	.0004

The above observations are strong evidence for a geminate recombination reaction occurring to the extent of about 10% under these conditions.

Higher acyl peroxides decompose thermally to yield different products. The decomposition of propionyl peroxide was shown to yield ethane, butane and ethylene (6). The butane, ethylene and part of the ethane were shown to come from a geminate recombination by the use of iodine scavenger.

DeTar (7) has decomposed thermally the acyl peroxide of optically active α-methyl-β-phenylpropionic acid.

$$\left(\phi\text{-}CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2\right)_2 \xrightarrow[CCl_4]{\triangle\ H} \text{products.}$$

The starting material had an optical rotation of + 7.5° and was 42% optically pure. The products obtained are given in Table III.

Table III

Product	Yield (moles/mole of peroxide)	rotation	optical purity
CO_2	1.41		
C_2Cl_6	0.2		
$\phi\text{-}CH_2CHClCH_3$	.6	0	
$\phi\text{-}CH_2CH(CH_3)CO_2H$	.04	+7.4	41%
Ester	.6	+9.6	
Acid Part		+7.8	44
Alcohol Part		+8.6	31

The ester, which is the major product on hydrolysis yielded an acid portion with 100% retention and an alcohol portion with 50% retention and 50% racemization. It was suggested that the ester was formed in a geminate recombination reaction. The possibility of an induced reaction was considered (see equation 1 page32 R = ϕCH_2CHCH_3). A model reaction studied by DeTar(8,32)is the decomposition of α-phenyl-valeryl peroxide. For this reaction the yield of ester was not affected for a 600 fold variation in peroxide concentration. The rate of formation of ester by the induced reaction should be affected by peroxide concentration while the geminate recombination should not.

Two other authors have studied the decomposition of acyl peroxides from optically active acids. These systems were complicated by the instability of the compounds involved and difficulties in product analysis.

Kharash (9) decomposed the acyl peroxide from α-methylbutyric acid (+17.3°, 96% optical purity).

$$\left[\begin{array}{l} CH_3 \\ H\text{-}\underset{|}{C}\text{-}CO_2 \\ C_2H_5 \end{array}\right]_2 \xrightarrow[\text{benzotrichloride}]{\triangle\ H} \begin{array}{l} CH_3 \quad CH_3 \\ H\text{-}\underset{|}{C}\text{-}CO_2\text{-}\underset{|}{C}\text{-}H \\ C_2H_5 \quad C_2H_5 \end{array}$$

$$\xrightarrow[H_2O]{KOH} \underset{C_2H_5}{\overset{CH_3}{H-C-CO_2H}} + \underset{C_2H_5}{\overset{CH_3}{H-C-OH}}$$

60% retention
40% racemization

ethylene glycol + 10° (56% optical purity) + 10.2° (78% optical purity)

Kharash felt that the acid had been racemized during the hydrolysis of the ester. The (+) acid and the (+) alcohol are of the same series.

Greene (10) attempted to prepare the peroxide of optically active α-phenylpropionic acid. The peroxide, however, decomposed faster than it formed. The products were normal for a peroxide decomposition.

$$\left[\begin{array}{c} CH_3 \\ | \\ H-C-CO_2 \\ | \\ O \end{array}\right]_2 \longrightarrow \text{ester + 2,3-diphenylbutane + acetophenone + styrene + α-phenylethanol}$$

The alcohol part of the ester was 20 - 50 % racemized.

The partial retention of activity in these products is interesting since Doering (11) has shown that free radicals do not normally retain asymmetry. Doering studied the decarbonylation of methylethylisobutylacetaldehyde by peroxide.

$$\underset{i\text{-Bu}}{\overset{CH_3}{C_2H_5-C-CHO}} \xrightarrow{\text{t-Bu peroxide}} \underset{i\text{-Bu}}{\overset{CH_3}{C_2H_5-C-H}}$$

αD(-.18°) inactive ±.01°

Winstein and Seubold (12) have shown that this reaction is a free radical reaction.

$$R\,CHO \xrightarrow{\text{peroxide}} R-\overset{O}{\overset{\|}{C}}\cdot \longrightarrow R\cdot + CO \xrightarrow{RCHO} RH + R\overset{O}{\overset{\|}{C}}\cdot$$

It is possible that in the decomposition of the optically active acyl peroxides the free radicals when formed do not have time to attain a statistical orientation before they recombine.

THERMAL DECOMPOSITION OF AZO COMPOUNDS

Several authors have studied the thermal decomposition of azo-bis-alkylnitriles in solution. This reaction has shown increased popularity, in the last ten years, as a free radical source for initiating polymerizations.

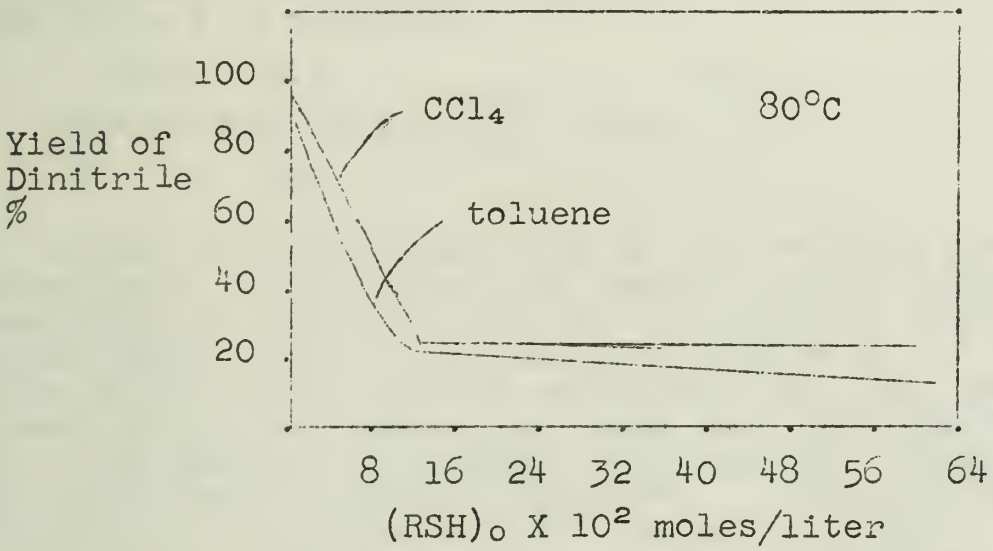
$$\underset{R^1}{\overset{CN}{R-C-}}N=N\underset{R^1}{\overset{CN}{-C-R}} \xrightarrow[\text{solvent}]{\triangle\ H} 2R\underset{R^1}{\overset{CN}{-C\cdot}} + N_2$$

The free radical formed is stabilized by resonance with the nitrile group. This stabilization reduces the reactivity of the radical to the extent that it will not abstract hydrogen from the solvent. The major product from the decomposition of 2,2'-azo-bis-isobutyronitrile (AIBN) is tetramethylsuccinonitrile (TMSN) and it is obtained in yields up to 96% (13).

Other products obtained under different conditions can be shown to result from a disproportionation reaction of the radicals (30).

Hammond (13) has studied this reaction in the presence of various scavengers. The yield of TMSN in the presence of increasing concentrations of n-butyl mercaptan is shown in Fig. 3.

Fig. 3



Even at high concentrations of mercaptan the formation dinitrile cannot be completely suppressed.

The rate of decomposition of AIBN has been shown to be first order. It has been measured by following the nitrogen evolution (14, 15, 16) by following the disappearance of absorption due to AIBN at 360, 370 and 380 mμ (17) and by following the disappearance of absorption due to scavengers present which react with the free radicals formed (13, 18). If there is a cage effect then the rate obtained by the first two methods will be different from that obtained by the last method. These two rates however will be related by a constant which is dependent on the proportion of reaction by each path.

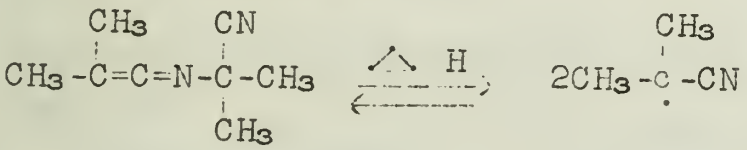
$$k_s = \underline{a}\, k_{N_2}$$

Hammond (13) measured the rate of formation of nitrogen and also the rate of disappearance of iodine present as a scavenger. The disappearance of iodine was followed spectrophotometrically using a wave length of 5000A. The rate obtained was independent of the initial iodine concentration. From these data $\underline{a}$ was calculated and was found to be .46 in carbon tetrachloride, .6 in benzene and .75 in nitrobenzene.

Hamill (19) has measured the yield of RI resulting from the decomposition of AIBN in benzene in the presence of iodine. By calculating the amount of decomposition based on the rate of nitrogen evolution he found $\underline{a}$ to be .6. This value was essentially constant

for iodine concentrations from .022 to .15 moles/liter. Bevington (20) has studied the decomposition of AIBN in toluene in the presence of DPPH. On the basis of yields of TMSN he found a to be .7. Walling (21) has reviewed the literature on rates of decomposition by various methods and has calculated a to be .7.

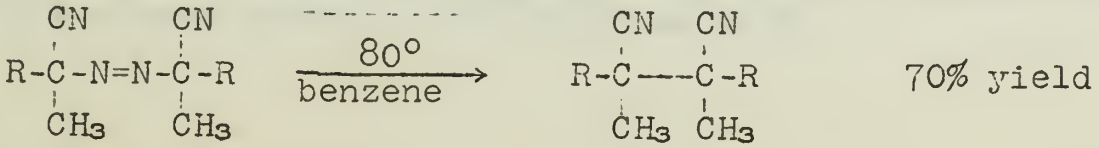
These results would indicate that some of the TMSN is being formed by either a cage reaction or another mechanism not involving radicals. Talat-Erben and Bywater (17) have found that an intermediate which absorbs at 320 mu forms during the decomposition of AIBN in toluene. This intermediate has an infra-red maximum at 4.96μ corresponding to a 1:2 diene structure. Hydrolysis products of the intermediate could be isolated in yields of 10 - 12% by interrupting the experiment at maximum absorption. The intermediate was thus shown to be a ketenimine.



It was calculated that 33% of the reaction goes through this intermediate. Talat-Erben and Bywater proposed that the ketenimine dissociated to give free radicals and finally reacted to yeild the product TMSN. Arnett (22) has used AIBN with C^{14} in the nitrile part of the molecule to study the efficiency of this compound as a polymerization initiator. He found that only 52% of the activity was in the polymer from methyl methacrylate. Thus only 52% of the radicals acted as polymer initiators. With other monomers higher efficiencies were obtained and with acrylonitrile the efficiency of AIBN became 100%. This has been considered as evidence for competition of the scavenger monomer with the diffusion controlled recombination (2).

Hamill (19) has studied the photochemical decomposition of AIBN in the presence of iodine scavenger using a mercury arc lamp. He found that the quantum yield measured as $2RI/N_2$ was dependent on the concentration of iodine through the concentration range .03 to .6 moles/liter. This would indicate competition of the scavenger reaction with the diffusion controlled reaction and the data do fit the theoretical treatment of such systems. It was found that the ratio $2RI/N_2$ was constant for the thermal reaction over the same iodine concentration range. Hamill, therefore, proposed that part of the TMSN in the thermal reaction is not formed by a radical mechanism. A possibility had been suggested by Hammond (13) that part of the TMSN resulted from a concerted reaction. The large effect of solvent cannot be explained, however, by this mechanism.

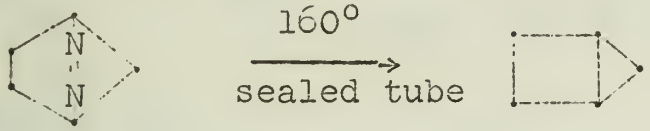
Overberger (23) has decomposed the dl and the meso forms of an azo-bis-nitrile. Both compounds gave identical products which were a mixture of the dl and the meso-dinitriles. The ratio of the products



R=isobutyl.

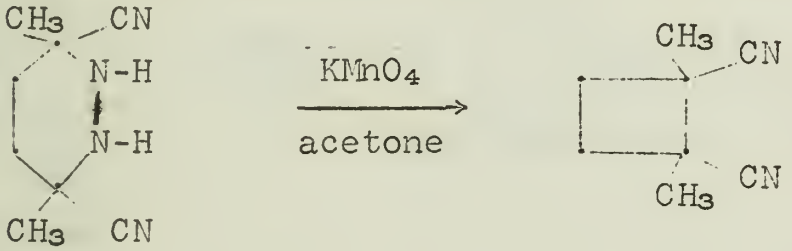
was 54:46 but it was not determined which was the dl and which was the meso. If part of the reaction went by a concerted mechanism the product would be different for the two experiments. The remaining mechanism possibilities are that the ketenimine yields TMSN by a concerted mechanism or that iodine is not a sufficiently efficient scavenger to compete with secondary recombination in the thermal reaction.

The use of azo compounds in ring closures has proven very useful recently. Criegee (24) was able to prepare bicyclo [2,1,0] pentane in the following way:



94% yield.

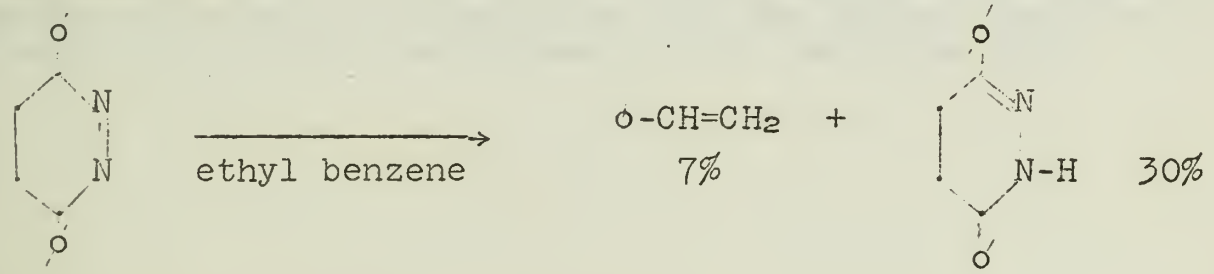
Overberger (25) has obtained a ring closure of this type:



43% yield

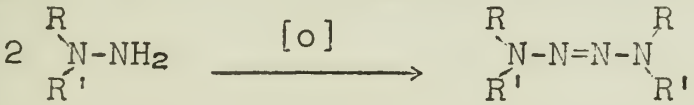
In both of these cases a biradical intermediate would be of the 1,4 type. Such biradicals are known to be unstable in that they readily split to form ethylenes. Large rings can also be formed (33).

Cohen (26) has, indeed, found such a splitting to occur in a similar reaction:

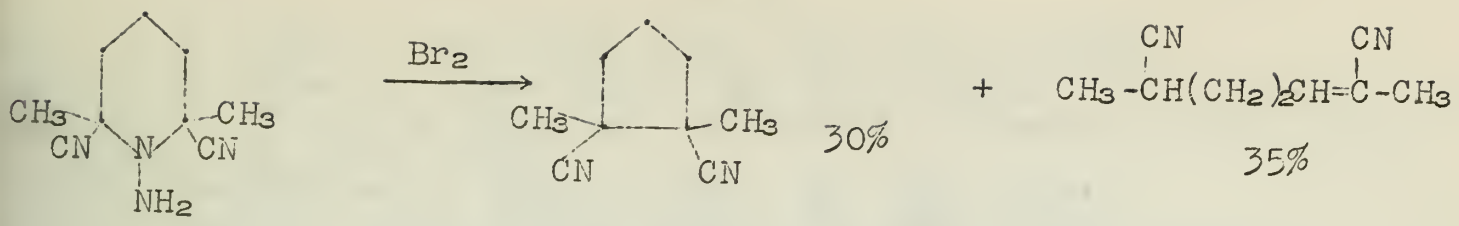


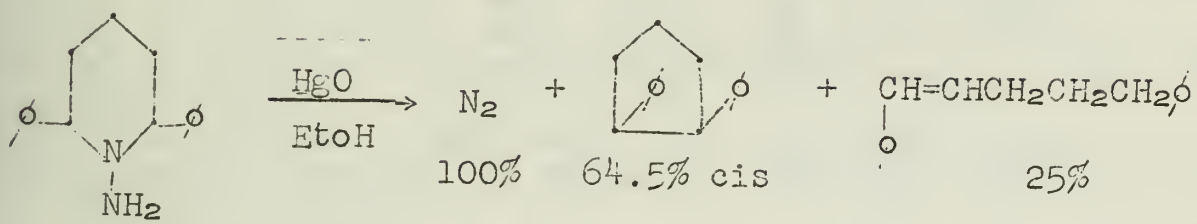
Diphenylcyclobutane was not isolated as a product.

Two reactions which may possibly have the same type of mechanism have been reported recently. The normal product of the oxidation of a 1,1 hydrazine is the tetrazine.

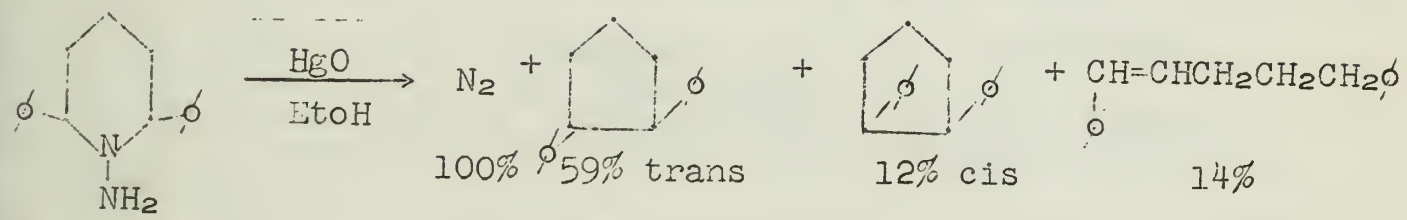


A few instances result in coupling of R and R'. Overberger (27, 28) obtained ring closure in the following ways:





phenyls cis



trans

The retention of configuration here also suggests a fast cage reaction or a concerted reaction. A concerted reaction would not be expected to give partial racemization as was found in the reaction of the trans starting material.

Recently a book, written by Walling, has been published. The author discusses many developements in free radical reactions in solutions with emphasis on polymerization reactions (31).

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VINYLLITHIUM AND MAGNESIUM COMPOUNDS

Reported by J. R. Larson September 30, 1957

INTRODUCTION

Although the first vinylmagnesium compound was prepared in 1902 (1), little application of these or of the corresponding lithium derivatives was made until recent years. These materials show promise as useful reagents in organic synthesis. It is the object of the present report to discuss the preparation, properties, and a few reactions of this interesting group of reagents.

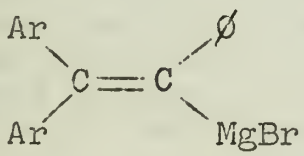
PREPARATION

I. Magnesium Compounds

The preparation of the Grignard reagent from α-bromostyrene was described by Tiffeneau in 1902. Later, in 1910, Rupe and Proske (2) increased the yield of this reagent by the use of iodine-activated magnesium. After hydrolysis, they obtained a 55% yield of styrene and 19% of the coupling product 1,4-diphenylbutadiene. By the use of this Grignard reagent, Meyer and Schuster (3) were able to prepare diphenylstyrylcarbinol in a 14% yield.

That the addition of another aromatic nucleus on the phenyl-bearing carbon increases the yield of Grignard was shown by Ziegler (4). He prepared 1,1-3,3-tetraphenylallyl alcohol (75% yield) by condensing β,β-diphenylvinylmagnesium bromide with benzophenone. It has been indicated by Hurd and Webb (5) that if the aryl groups are anything but phenyl, a great deal of coupling to form butadienes occurs. The use of magnesium-copper alloy, however, allowed the formation of the Grignard reagent from phenyl-p-tolylbromoethylene in 51% yield.

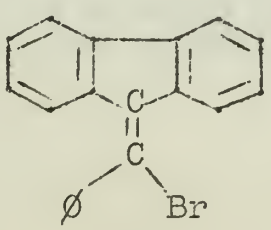
Several triarylvinylmagnesium reagents, having the general structure (I) were prepared by Koelsch (6,7).



I

where Ar = Ø, p-tolyl, and p-anisyl

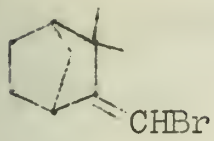
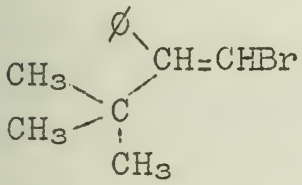
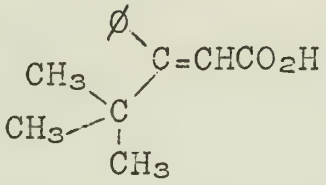
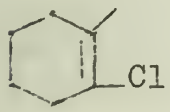
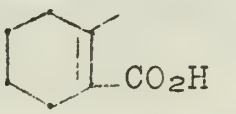
He also made the Grignard reagent from α-phenyl-β-diphenylenevinyl bromide (II) in high yield.



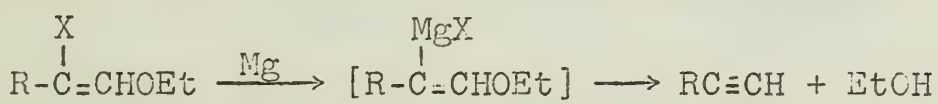
II

Some other vinylmagnesium compounds prepared before 1950 are shown in Table I. The yields are generally low.

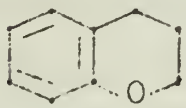
Table I

Halide	Reactant	Product	Yield	Ref.
	CO_2		20%	8
	CO_2		--	9
$(CH_3)_2C{=}CHBr$	CH_3CHO $(CH_3)_2CHCHO$ $\emptyset CHO$ H_2O	$(CH_3)_2C{=}CHCHOHCH_3$ $(CH_3)_2C{=}CHCHOHCH(CH_3)_2$ $(CH_3)_2C{=}CHCHOH\emptyset$ $(CH_3)_2C{=}CH_2$	14% 14% -- --	10 10 12 10
$(CH_3)_2C{=}C(CH_3)Br$	CH_3CHO	$(CH_3)_2C{=}C(CH_3)CHOHCH_3$	--	12
$C_5H_{11}CH{=}CHBr$	H_2O	$C_5H_{11}CH{=}CH_2$	20	13
	CO_2		--	14

A method for the preparation of vinylmagnesium compounds was reported by Normant (15,42) in 1954. He observed that the treatment of β-halo vinyl ethers with magnesium in tetrahydrofuran resulted in the formation of an alcohol and an acetylenic hydrocarbon. He assumed that first step of the reaction was the formation of the Grignard reagent, but that the presence of the alkoxyl group in the β-position facilitates an elimination to the acetylene. It seemed



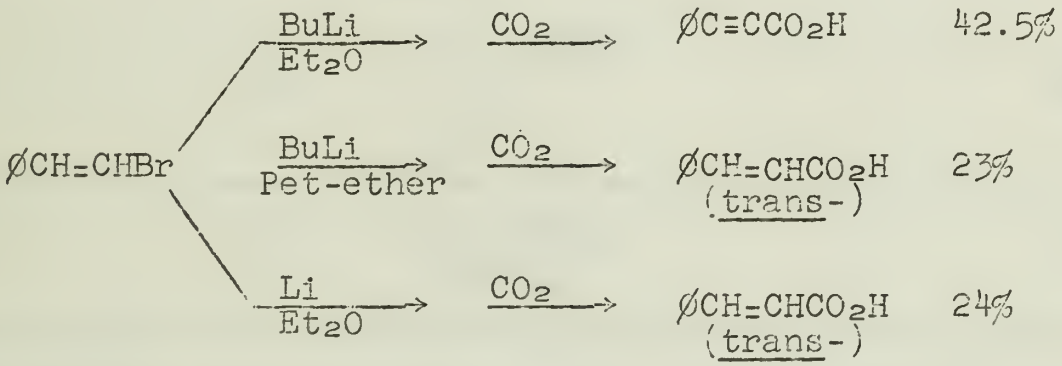
reasonable that the vinyl halides might also form Grignard reagents readily in this solvent. The idea proved fruitful; he prepared many vinyl Grignard reagents in high yields using ordinary magnesium and temperatures. Some of the reagents prepared are shown in Table II.

Halide	Reactant	Product	Yield	Ref.
$CH_3CH{=}CHBr$	H_2O	$CH_3CH{=}CH_2$	90%	15
$C_5H_{11}CH{=}CHBr$	H_2O	$C_5H_{11}CH{=}CH_2$	71%	15
$\phi CHBr{=}CH_2$	H_2O	$\phi CH{=}CH_2$	63%	15
ϕCl	H_2O	ϕH	95%	15
	H_2O		74%	15

II. Lithium Compounds

Following treatment of ω-bromostyrene with butyllithium in petroleum ether for 38 days, Marvel, Hager, and Coffman (25) obtained styrene and 1,4-diphenylbutadiene; β-styryllithium presumably being an intermediate in each case. In 1936, Wright (16) treated the same bromide with metallic lithium and, after carbonation of the reaction mixture, obtained 24% of trans-cinnamic acid and 6% of phenylpropiolic acid. Direct hydrolysis of the lithium reagent led to similar yields of styrene and phenylacetylene. By treating the same reagent with dibenzalacetone, Marvel, Mueller, and Peppel (26) obtained a 33% yield of tristyrylcarbinol.

It was discovered by Gilman, Langham and Moore (27) in 1940, that treatment of ω-bromostyrene with butyllithium in ether followed by carbonation afforded phenylpropiolic acid. The same reaction in petroleum ether gave trans-cinnamic acid.

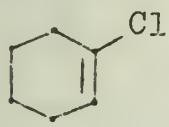
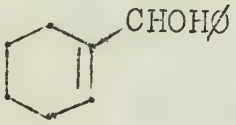
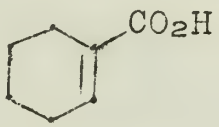
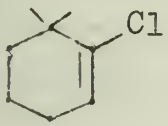
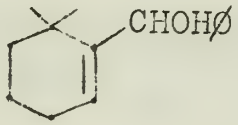
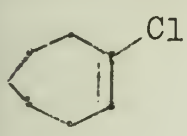
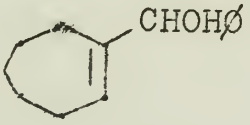
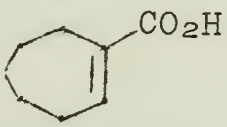


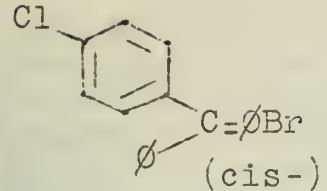
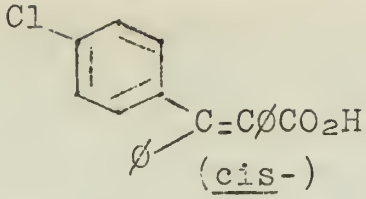
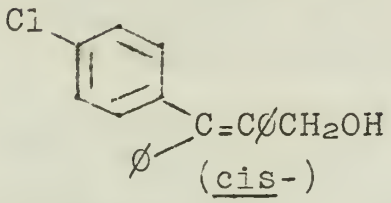
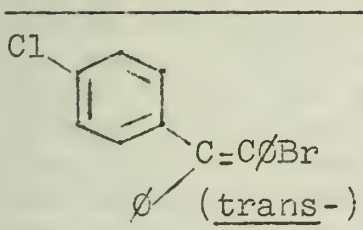
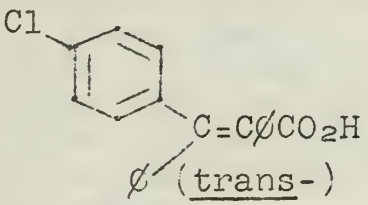
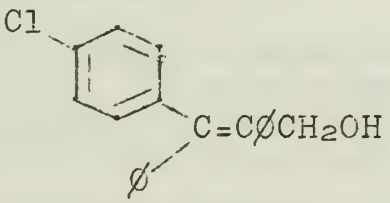
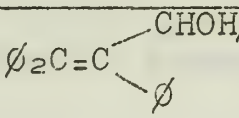
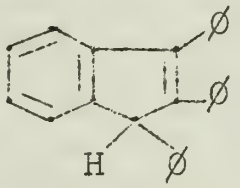
Aliphatic vinyllithium compounds were not investigated until 1950 when Braude, Coles, and Timmons (17) prepared several of these reagents. By allowing the vinyl halides to react with metallic lithium in refluxing ether, they were able to make lithium reagents from propenyl bromide, isobutenyl bromide and chloride, cyclohexyl chloride, 6,6-dimethylcyclohexenyl chloride, and cycloheptenyl chloride in yields averaging about 35%.

By the use of butyllithium in place of metallic lithium, Curtin, Harris, Johnson, and Steiner (21-23) found that the yields of lithium reagents from the di- and triarylvinyl bromides are from 60% to 80%. Carbonation of the lithium reagent from α-bromostyrene gave the cinnamic acid in 55% yield, but ω-bromostyrene, as observed previously, furnished 45% of phenylpropiolic acid.

Table III contains a representative list of vinyllithium reagents which have been prepared.

Table III

Halide + Li	Reagent	Product	Yield	Ref.
$CH_3CH{=}CHBr$	ØCHO	$CH_3CH{=}CHCHOH\text{Ø}$	35%	20
$(CH_3)_2C{=}CHBr$	ØCHO	$(CH_3)_2C{=}CHCHOH\text{Ø}$	33%	18
	CO_2	$(CH_3)_2C{=}CHCO_2H$	7%	18
	ØCHO		40%	19
	CO_2		5%	19
	ØCHO		63%	28
	ØCHO		48%	29
	CO_2		39%	29
$\text{Ø}CH{=}CHBr$	CO_2	$\text{Ø}CH{=}CHCO_2H$ (trans-)	24%	6
Halide + BuLi				
$\text{Ø}CH{=}C\text{Ø}Br$ (cis-)	CO_2	$\text{Ø}CH{=}C\text{Ø}CO_2H$ (cis-)	58%	22
$\text{Ø}CH{=}C\text{Ø}Br$ (trans-)	CO_2	$\text{Ø}CH{=}C\text{Ø}CO_2H$ (trans-)	62%	22

	CO_2		82%	23
	CH_2O		69%	21
	CO_2		62%	23
	CH_2O		73%	21
$Ø_2C=C(Ø)Br$	ØCHO	 isolated as 	65%	21

STEREOCHEMISTRY

A great deal of work has been done in the study of the stereochemistry of the reactions of vinyllithium compounds, while the vinylmagnesium compounds have been somewhat neglected.

The first indication of the stereochemistry of vinylmetallic compounds emerged when Wright (16) carbonated the lithium reagent prepared from the equilibrium mixture of ω-bromostyrenes and obtained 24% of trans-cinnamic acid but no cis-acid. The magnesium compound from this mixture furnished 12% of the trans-acid and 19% of the cis-acid. From cis-ω-bromostyrene he obtained 19% cis-cinnamic acid and 9% trans-cinnamic acid. The trans-bromide gave 30% trans- and 20% cis-cinnamic acid. It is interesting that the equilibrium mixture of the bromides gives more cis- than trans- acid, since Dufraisse (24) reported the mixture to consist mainly of the trans- bromide.

Cis- and trans-2-(p-chlorophenyl)-1,2-diphenylvinyl bromides were prepared by Koelsch (6,7) and allowed to react with magnesium. After carbonation, both isomers gave mixtures of cis- and trans-3-(p-chlorophenyl)-2,3-diphenylacrylic acids, with the cis- acid predominating in the mixture from the cis- bromide, and the trans- acid in that from the trans- bromide. Treatment of the same bromides with butyllithium, followed by carbonation, was found by Curtin and Harris

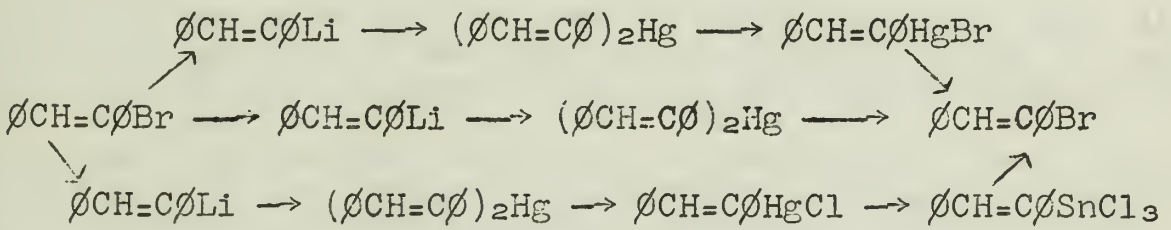
(23) to yield only the isomer resulting from stereospecific reaction; the trans- bromide gave 69% of trans- acid, and the cis- bromide furnished the cis- acid in 82% yield. Treatment of these lithium reagents with methanol gave the expected hydrocarbons in 100% crude yield. An extension of this work was reported by Curtin, Johnson, and Steiner (21) in 1955. They treated the same bromides mentioned above with formaldehyde, benzophenone, and methyl iodide; again the reactions were observed to be highly stereospecific in nature.

The preparation of cis-propenyllithium was reported by Braude and Coles (20) in 1951. The reagent after treatment with benzaldehyde, crotonaldehyde, and acrolein, furnished only the cis- alcohols. Since the trans- lithium reagent was not tried, it left some doubt as to whether the reaction was stereospecific, or if the trans- bromide might yield the same products. In order to clarify this point, Curtin and Crump (31) prepared both the cis- and the trans- bromides. Reaction of these with metalic lithium followed by treatment with benzaldehyde showed 100% stereospecificity for the cis- isomer, and at least 90% for the trans- isomer.

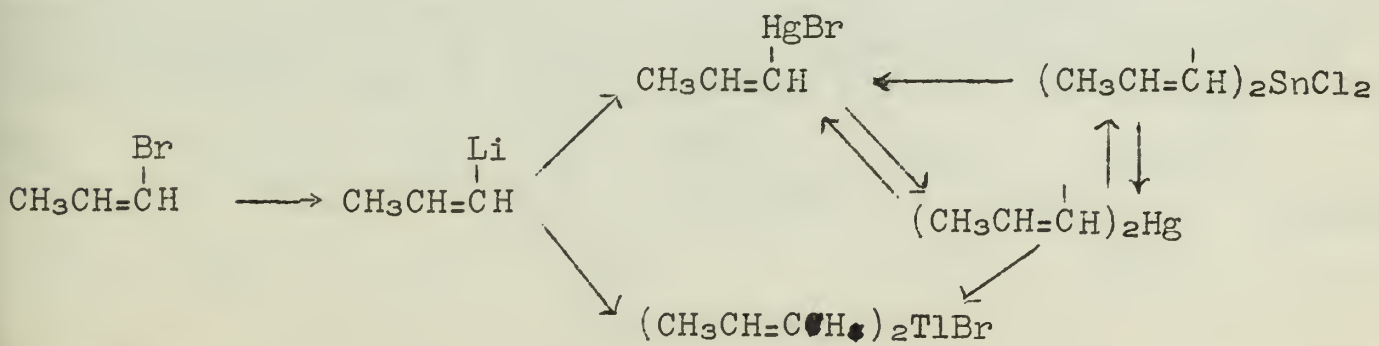
Cis- and trans-2-bromo-2-butene have been treated with both lithium and magnesium (32,33). In both cases the products were mainly those expected. Small amounts of isomerized products were found, but the starting bromides may not have been pure.

There seems to be no doubt then that the reactions of both vinyllithium and vinylmagnesium reagents follow a stereospecific course.

Additional information on this subject has been added by Nesmeyanov and Borisov (34). In an attempt to prove that the reactions of vinylmetallic compounds proceed with retention of configuration and not with inversion, they have investigated a large number of these reactions. The end products were always stereochemically identical with the starting materials. The reaction sequences are as follows:



and



REACTIONS

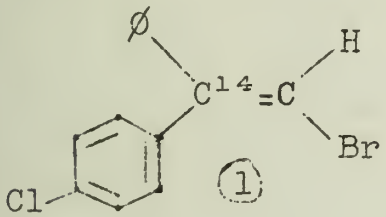
In general the reactions which vinylmagnesium and vinyllithium reagents undergo are the same as those of the normal Grignard and

lithium reagents (35-48). The remainder of this report will discuss a few of the more unusual reactions observed with these compounds.

One of the most interesting reactions of the vinyllithium reagents is the formation of phenylpropiclic acid when ω-bromostyrene is treated in ether with butyllithium and then carbonated. If β,β-diphenylvinyl bromide is treated with butyllithium in ether, the same type of reaction is encountered (49). Tolan is isolated in 43% yield along with β-phenylcinnamic acid (30%) and n-butyl-2,2-diphenyl

$$\phi_2C{=}CHBr + BuLi \xrightarrow{Et_2O} \xrightarrow{CO_2} \phi C{\equiv}C\text{-}\phi$$

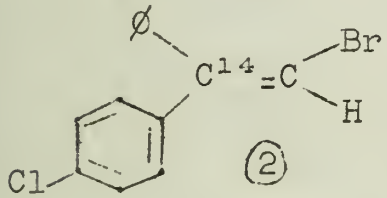
vinyl ketone. Diarylacetylenes are also formed from cis- and trans-2-(p-chlorophenyl)-2-phenylvinyl bromide. It is interesting that the group trans- to the leaving bromide is the one which migrates. This was shown by using C^{14} labeled bromide and oxidizing the products to the corresponding benzoic acids.



(1)

+ BuLi $\xrightarrow{Et_2O}$ $\xrightarrow{CO_2}$ 

(92% Phenyl migration)



(2)

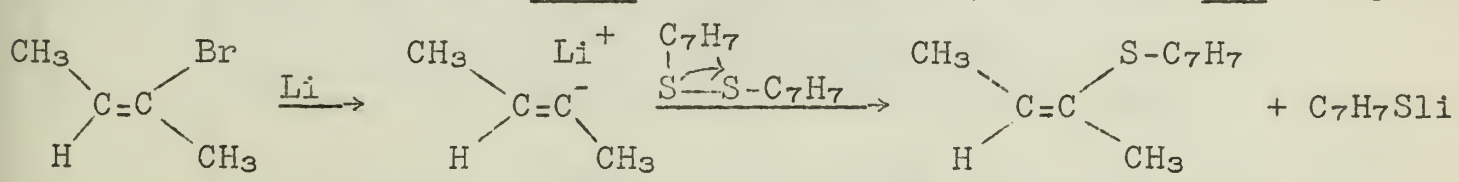
+ BuLi $\xrightarrow{Et_2O}$ $\xrightarrow{CO_2}$ $\phi C^{14}{\equiv}C\text{-}\phi$

(82% p-chlorophenyl migration)

(Containing about 20% of (2))

These tolan forming reactions seem to occur whenever there is a hydrogen atom present on the halogen-bearing β-carbon. In such cases, metallic lithium must be used to produce the vinyllithium reagent.

One more interesting reaction is that between the lithium derivatives of cis- and trans-2-bromobutenes and p-tolyl disulfide. The products are cis- and trans-2-p-tolylthio-2-butenes (50). Bordwell and Landis state that these reactions may be looked on as nucleophilic displacements of the 2-butenyl-2-carbanion (configuration maintained) on one of the sulfur atoms of p-tolyl disulfide. The yields were 52% from the trans- bromide and 62% from the cis- compound.



+ C_7H_7SLi

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THE STRUCTURE OF PICROTOXIN

Reported by Wilmon B. Chipman October 3, 1957

I. INTRODUCTION:

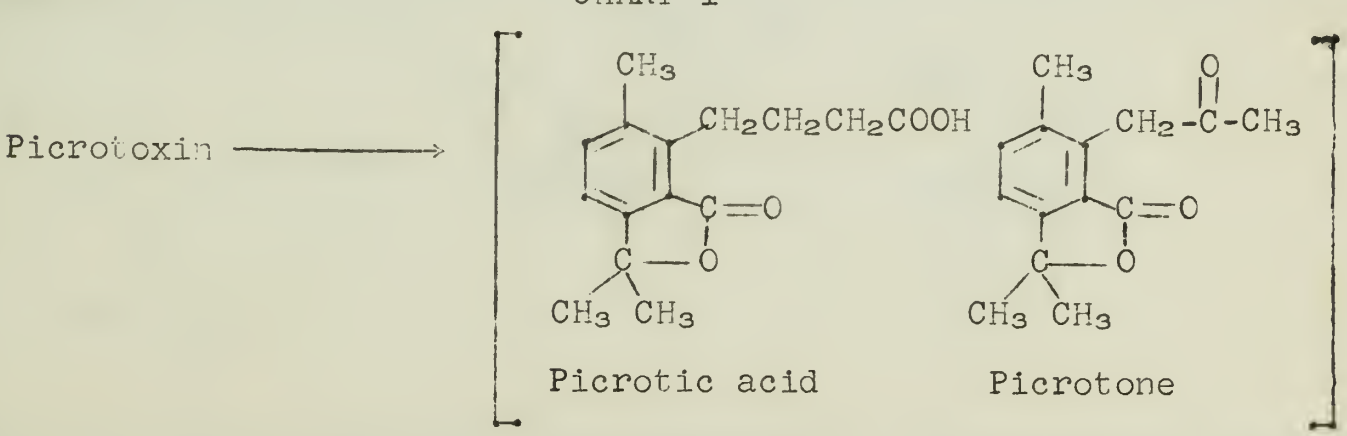
Picrotoxin, a physiologically active amaroid (non-nitrogenous bitter principle), was first isolated from the fruit of the shrub Anirnita Cocculus (1). Picrotoxin is a complex of the physiologically inactive picrotin ($C_{15}H_{18}O_7$) and the physiologically active picrotoxinin ($C_{15}H_{16}O_6$)(2). Recent X-ray and melting point studies show that the complex is equimolar (3). The earlier chemistry of picrotoxin has been reviewed in both the MIT and the Illinois seminars (4). This seminar will consider only that earlier chemistry which is pertinent to more recent studies.

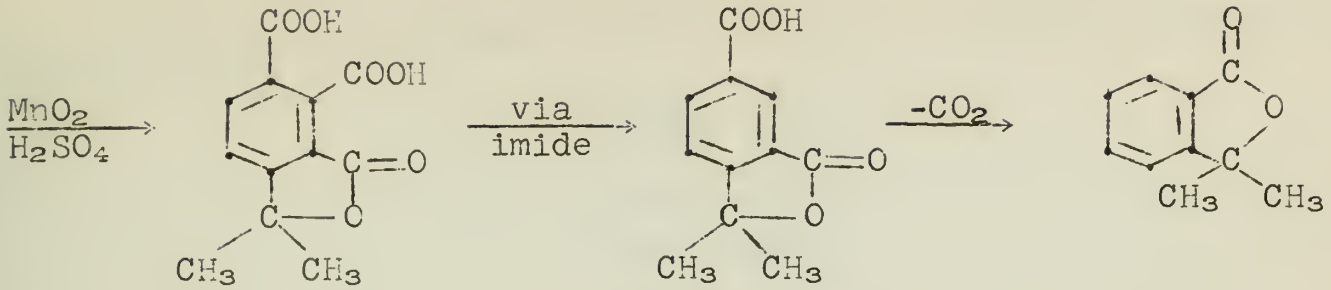
Picrotoxinin may be isolated from the complex by bromination, affording a mixture of two stereoisomeric monobromo derivatives (arbitarily named α-bromopicrotoxinin and β-bromopicrotoxinin). Debromination of the mixture of isomers with zinc yields pure picrotoxinin. Since this is the customary isolation procedure, all of the efforts to establish structure have been concerned with picrotoxinin. Picrotoxinin has one double bond; picrotin differs from picrotoxinin by the elements of one molecule of water and is saturated. Hence it is generally accepted that picrotin differs from picrotoxinin only in the hydration of the double bond.

II. SKELETAL STRUCTURE:

Acid Degradations: The first major step toward the elucidation of the structure of picrotoxin was the degradative work of Robertson, et al (5). Treatment of picrotoxin with phosphorus and boiling HI yielded picrotic acid ($C_{15}H_{18}O_4$) and picrotone ($C_{14}H_{16}O_3$). Oxidation of either of these two products gave a dibasic acid, $C_{12}H_{10}O_6$, identical with that previously obtained by Hansen from the MnO_2-H_2SO_4 oxidation of picrotoxin. Degradation of this acid via the imide gave a monobasic acid, $C_{11}H_{10}O_4$, identical with the known cannabinolactonic acid. Decarboxylation of this acid afforded α,α-dimethylphthallide. The above sequence of reactions was then formulated as follows:

CHART I

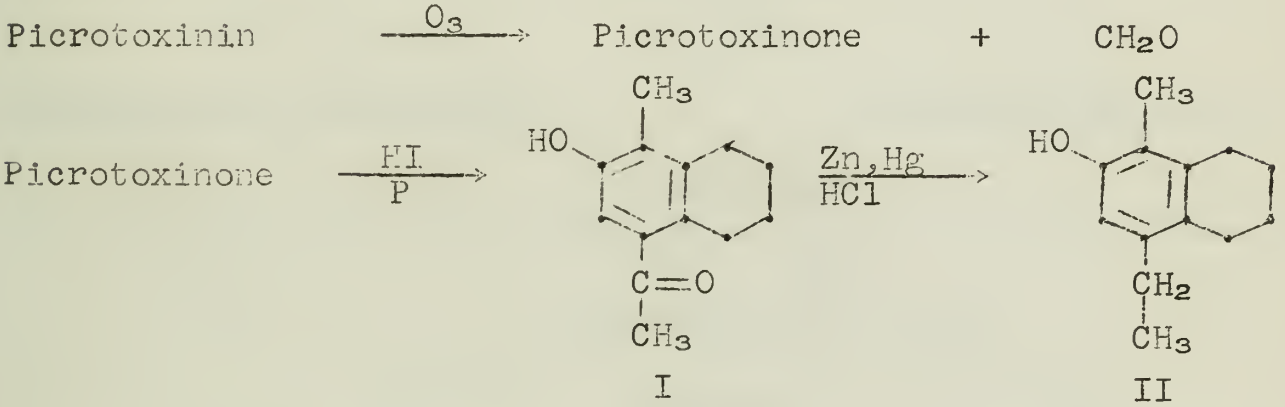




Cannabinolactonic acid

Harland and Robertson established the existance of a terminal methylene group in picrotoxinin by the following sequence of reactions.

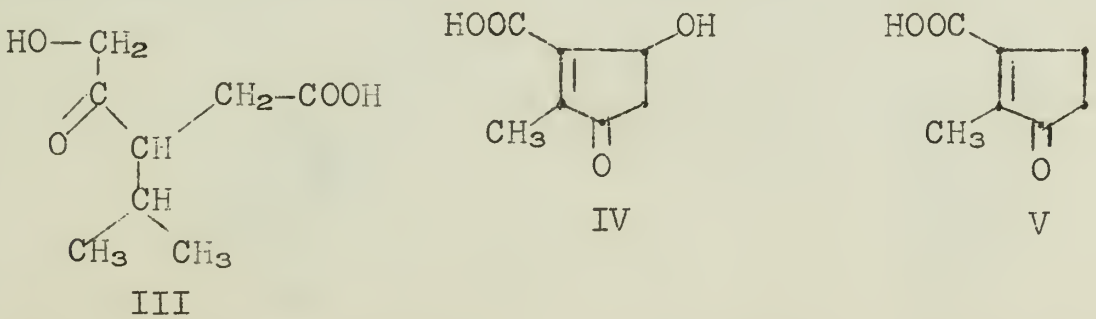
CHART II



Ozonization of Picrotoxinin yielded picrotoxinone ($C_{14}H_{14}O_7$) and formaldehyde. Treatment of picrotoxinone with HI and phosphorus afforded the phenolic ketone, I, and Clemmensen reduction of this compound gave the phenol, II, which was synthesized independantly. Establishment of the structures of I and II, together with the existence of an isopropyl side chain in several degradation products (vide infra) would indicate that the double bond occurs in the side chain.

Alkaline Degradations: Sutter and Schlittler have investigated the alkaline degradation of α-dihydropicrotoxinin, the product resulting from catalytic reduction of picrotoxinin (7). Gentle alkaline hydrolysis gave two acids, III and IV, which were identified by independent synthesis.

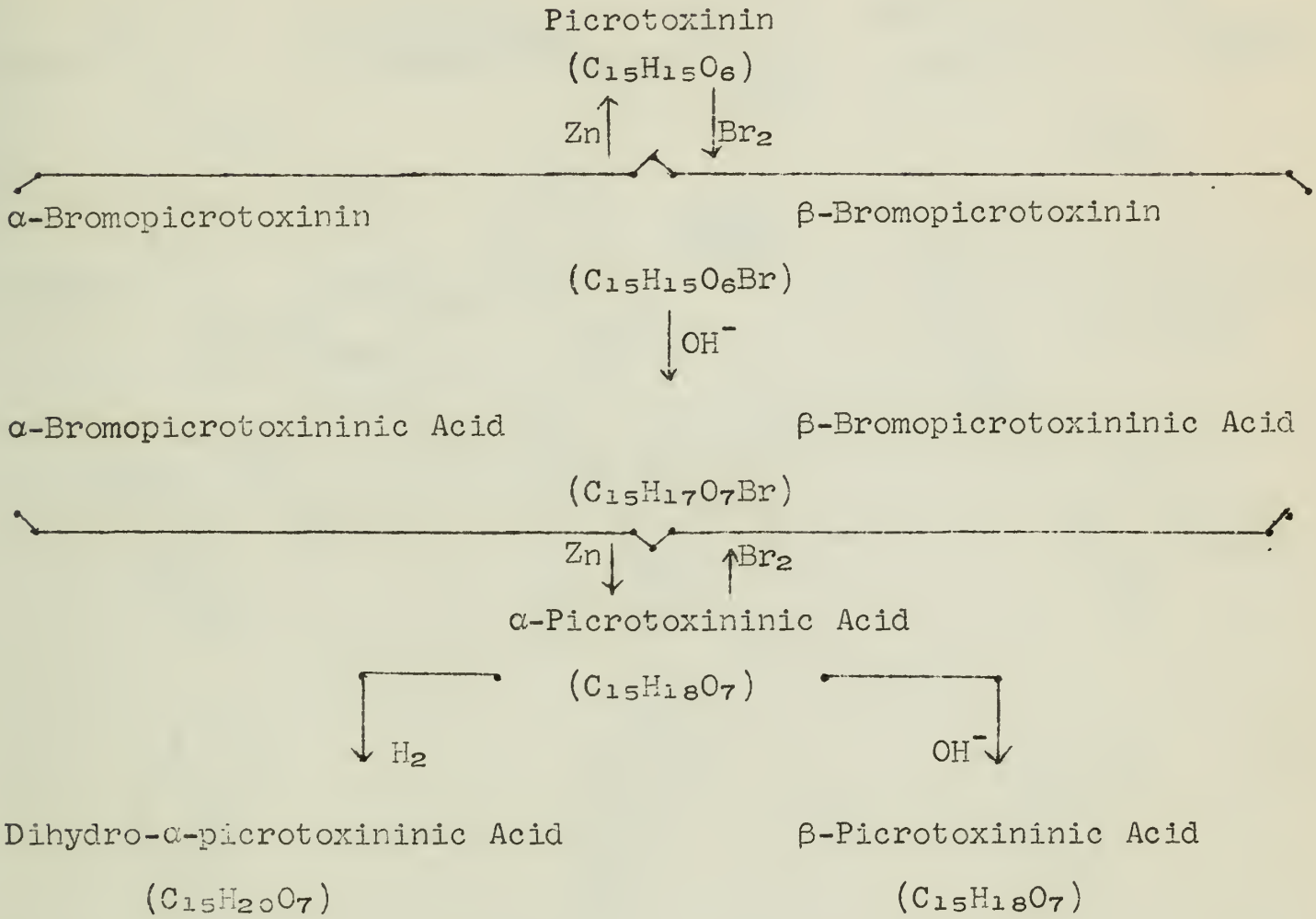
CHART III



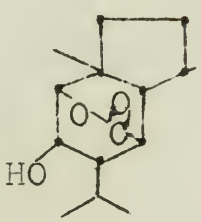
Barium hydroxide hydrolysis of picrotoxinin afforded carbon dioxide, IV and the unsaturated keto-acid, V, which was identified by conversion to the known 2-methylcyclopentanoic acid.

Conroy has investigated the pyrolysis of dihydro-α-picrotoxininic acid (8, 9).

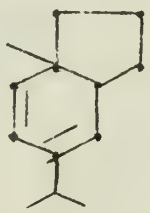
CHART IV



The synthesis of this compound is outlined in the above table, where the α's and β's are an arbitrary designation for isomeric products. The pyrolysis product, picrotoxinide, absorbed one mole of hydrogen over platinum oxide, affording the saturated ketone dihydropicrotoxinide. Treatment with ethane-1,2-dithiol followed by Raney-nickel desulfurization gave a product formulated as VI, since on conversion to the benzoate followed by pyrolysis the product isolated was picrotoxadiene, VII.



VI

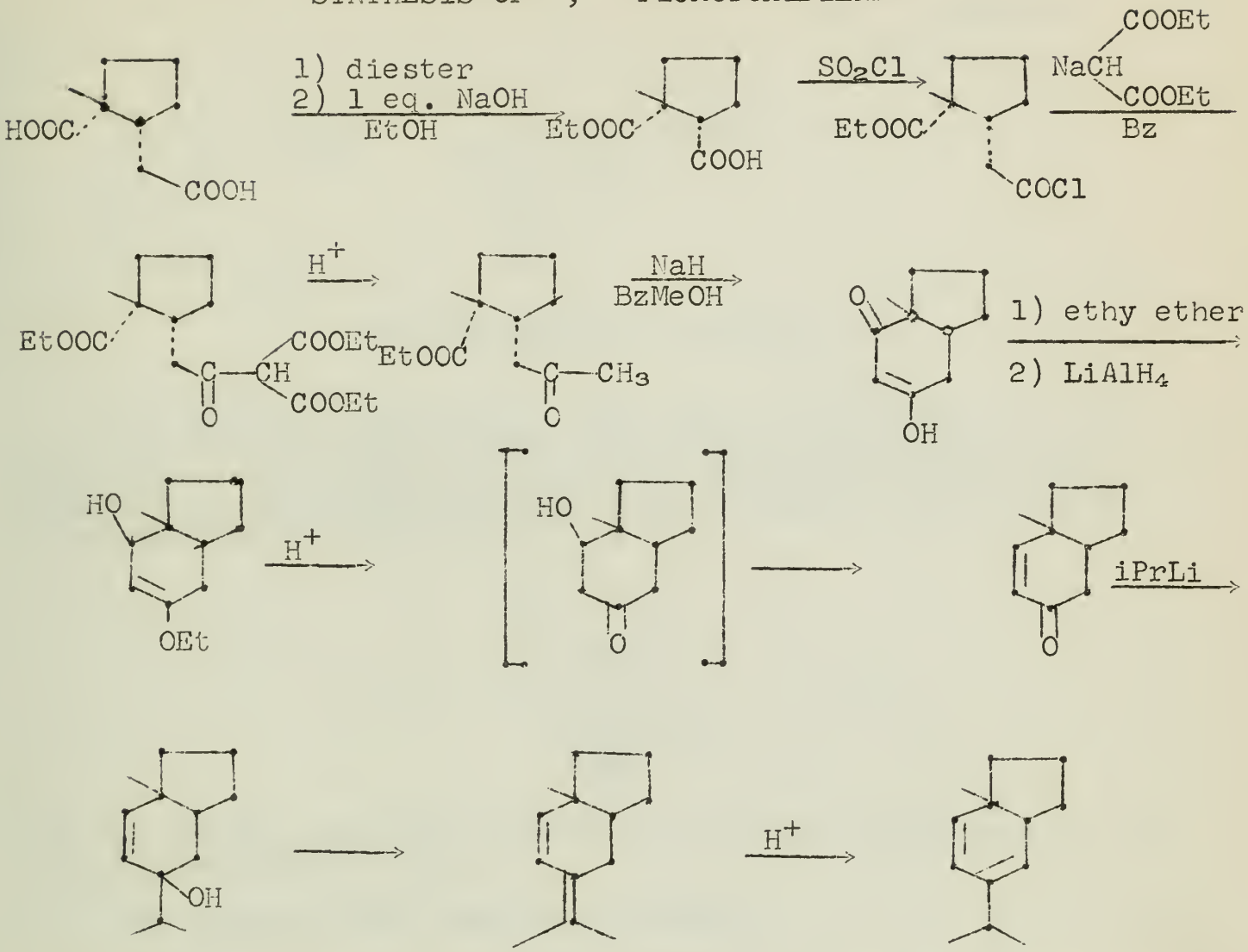


VII

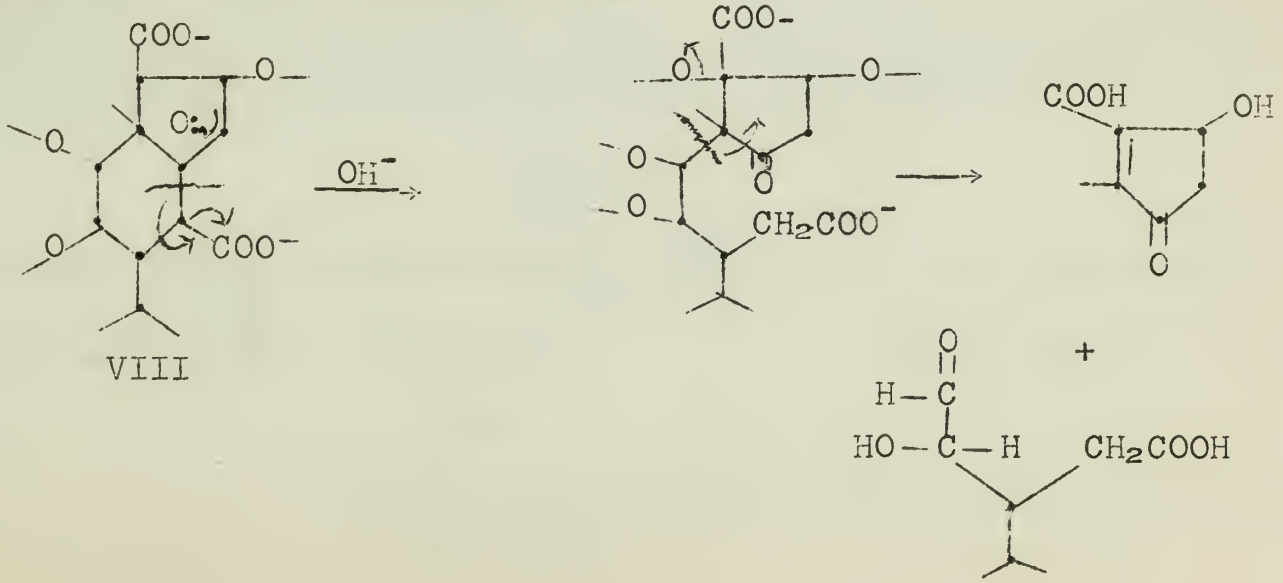
The structure of VII was established by the indepent synthesis shown in Figure I. The position of the lactone bridge as shown above is based on spectral evidence.

FIGURE I

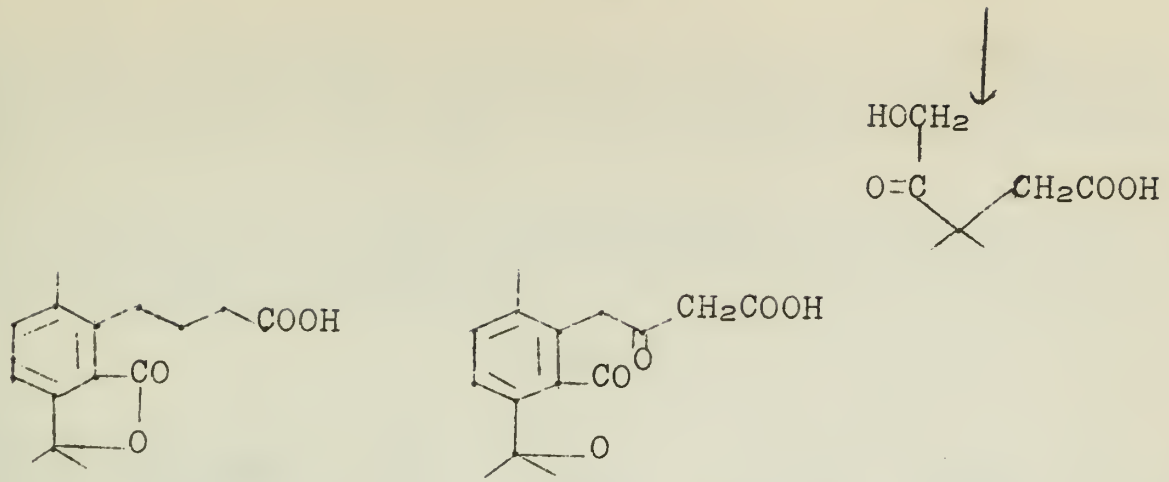
SYNTHESIS OF , -PICROTOXIDIENE



STRUCTURES BASED ON DEGRADATIVE EVIDENCE: Conroy has postulated the partial structure VIII for α-dihydropicrotoxinin on the basis that the alkaline degradation products can be accounted for as resulting from two reverse aldol condensations, and that the acid degradation products can also be accounted for.

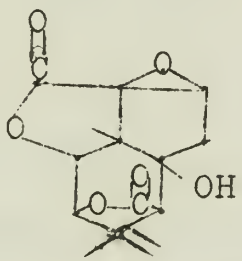


VIII



Acid Degradation Products

The symbol —O— represents the point of attachment of the lactones and the ether bridge; the positions of these groups are not specified. On the basis of the above mechanism and the known reactions of picrotoxinin Conroy has postulated the following structure for picrotoxinin.



The New Zealand group has postulated a similar mechanism for the alkaline degradation (10).

III THE NATURE OF THE FUNCTIONAL GROUPS:

It has been generally accepted that four of the oxygen atoms of picrotoxinin form two lactone groups, that the fifth exists as a tertiary hydroxyl group, and that the sixth exists as an ether (4). Considering the multiplicity of functional groups in the molecule, it is not unexpected that a considerable amount of confusion has occurred on this point. The New Zealand group (11) has investigated the nature of the functional groups in the compounds shown in the following chart and in Chart IV.

CHART V

Picrotoxinin ($C_{15}H_{16}O_6$) $\xrightarrow[\text{or } H^+]{H_2/Pd}$ Neopicrotoxinin ($C_{15}H_{16}O_6$) $\xrightarrow{Br_2}$ Bromoneopicrotoxinin ($C_{15}H_{15}O_6Br$)

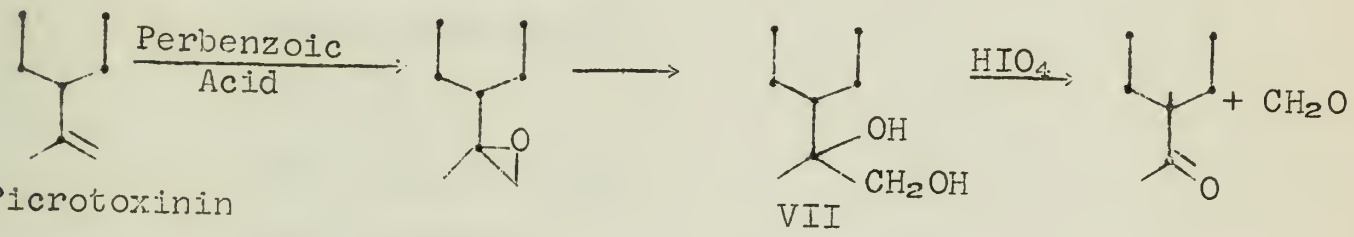
Neopicrotoxinin ($C_{15}H_{16}O_6$) $\xrightarrow{H_2}$ β-dihydropicrotoxinin ($C_{15}H_{18}O_6$)

Bromoneopicrotoxinin ($C_{15}H_{15}O_6Br$) $\xrightarrow{OH^-, \triangle}$ Bromoneopicrotoxinic Acid ($C_{15}H_{17}O_7Br$)

The rapid isomerization of picrotoxinin in the presence of palladium and hydrogen (or mineral acids) has been explained on spectral evidence as a shift of the terminal double bond into the position endo- to the ring.

The Double Bond: The New Zealand group has confirmed the existance of a terminal double bond in picrotoxinin by the sequence of reactions shown in Chart VI.

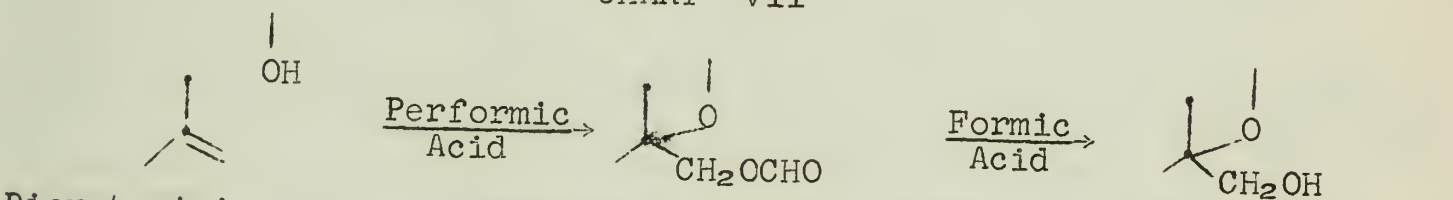
CHART VI



Picrotoxinin VII

The hydroxylation of the double bond of picrotoxinin with performic acid has also been investigated.

CHART VII



Picrotoxinin Hydroxypicrotoxinin formate Hydroxypicrotoxinin

Hydroxypicrotoxinin formate is stable to periodic acid and lead tetraacetate. The oxide ring has been formulated as on the tertiary rather than the primary carbon for two reasons. Picrotoxinin and neopicrotoxinin brominate similarly, hence the oxide ring is probably formed on the same carbon atom in both compounds. (O'Donnell and Robertson had earlier reported the participation of the hydroxyl group in bromination (12)). Hydroxypicrotoxinin forms a mono acetate which is oxidized by chromium trioxide-acetic acid.

The Hydroxyl Group: The New Zealand group has also carried out a series of acylation and active hydrogen studies on the same series of compounds (11). A systematic study of acetylation reactions has been made as the earlier work on this subject gave rather erratic results. The results are shown in Table III.

TABLE III

ACETYLATION OF	PICROTOXININ DERIVATIVES
Hydroxy picrotoxinin	1
Picrotin	2 (1)
Dihydropicrotoxinin	2
Dihydroxypicrotoxin	3
Picrotoxinin	0

Dihydroxypicrotoxinin (VII, Chart VI) unexpectedly gives a triacetate (only one acetylatable hydroxyl has been added to picrotoxinin); and dihydropicrotoxinin similarly gives a diacetate. The results of active hydrogen determinations are given in Table IV.

TABLE IV

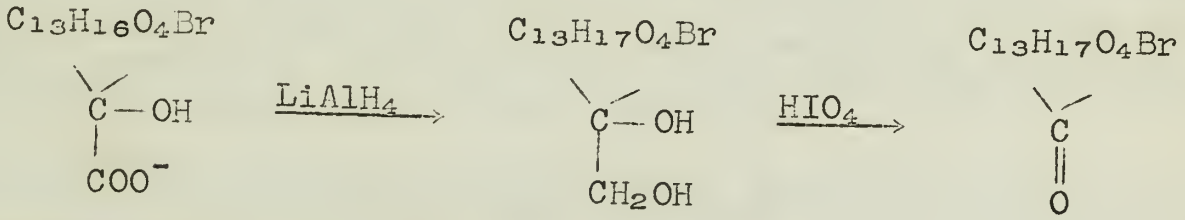
NUMBER OF ACTIVE HYDROGENS OF PICROTOXININ DERIVATIVES

Picrotoxinin	2
Dihydropicrotoxinin	4
Picrotin	2
β-Bromopicrotoxinin	1
Neopicrotoxinin	3

Picrotoxinin has two active hydrogens, one of which must take part in bromination. Dihydropicrotoxinin has four active hydrogens, a value which is unexpected, since reduction of the double bond should not raise the number of active hydrogens. Picrotin unexpectedly shows two active hydrogens. It should be noted that acetylation studies give a minimum figure for the number of hydroxyl groups, and that active hydrogen determinations give a maximum. In a complex molecule it is difficult to decide if there are groups other than hydroxyl which can give active hydrogens. There is an evident conflict in the evidence of the function of the sixth oxygen atom.

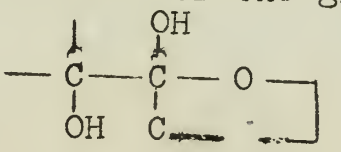
The Lactone Groups-Centers of Acidity: Conductometric titrations by the New Zealand group establish the presence of two titratatable centers of acidity in picrotin and picrotoxinin. Lithium aluminum hydride reduction of β-bromopicrotoxininic acid, followed by periodate oxidation of the resulting polyhydroxy alcohol, affords a 95% yield of a crystalline ketone, $C_{14}H_{17}O_5Br$.

CHART VIII



β-Bromopicrotoxininic Acid

The periodate oxidation of reduced β-bromopicrotoxinin takes place in two stages, the second of which involves the expulsion of bromine. The consumption of one mole of periodate produces from the neutral starting material one mole of back-titratable (lactonic) acidity. This is taken as evidence for the grouping

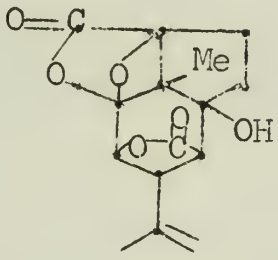


which on periodate cleavage would generate ketone and lactone functions.

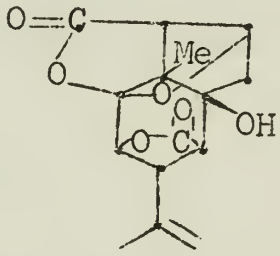
Conroy has postulated the existance of two five-membered lactones on spectral evidence (8).

THE POSITIONS OF THE FUNCTIONAL GROUPS:

The New Zealand group has postulated that one of the two following structures is the structure of picrotoxinin (11).



or



Their reasoning is as follows. One of the two titratable centers of acidity is an acidic hydroxyl, not a lactone. Three facts support this argument.

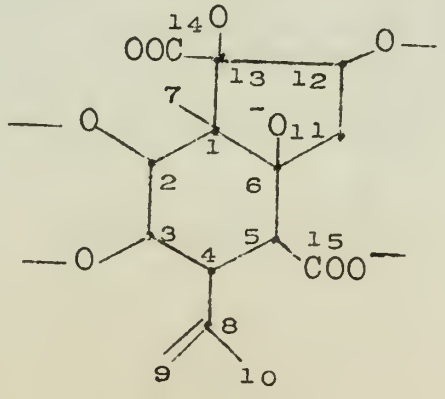
a) Both bromopicrotoxinin and hydroxypicrotoxinin are monobasic; the less of an active hydroxyl from picrotoxinin corresponds to the less of one unit of acidity.

b) Reduced picrotoxinin, which has no carbonyl absorbtion and hence cannot be lactonic, titrates as a monobasic substance.

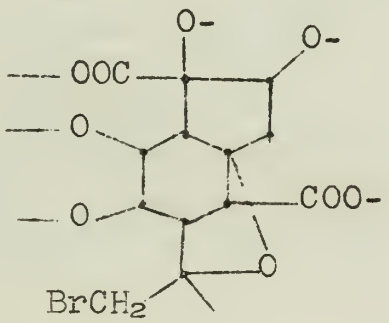
c) Both bromopicrotoxinin and reduced picrotoxinin yield monomethyl ethers with diazomethane.

If one of the two titratable centers of acidity is an acidic hydroxyl, then one of the two lactones must be stable to alkali. The formulation of a hemiacetal type lactone in the two postulated formulas is consistent with this hypothesis, since this group has been shown in several cases to be stable to alkali (13). The infrared spectra of this group of compounds show a band at 1780-1760 cm.$^{-1}$ which has been attributed to the hemiacetal type lactone. The possibility of the ether group being present as an epoxide (Conroy formula) has been ruled out on the basis that this group would suffer fission under these conditions.

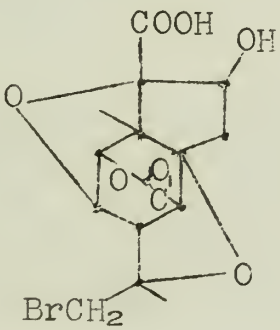
Basing his arguments on the partial structure of picrotoxinin shown below, Conroy has proposed structures for the two degradation



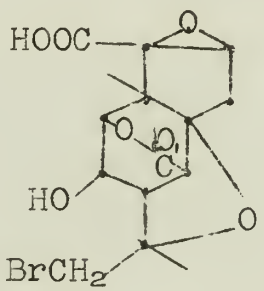
products, α-picrotoxininic acid and β-bromopicrotoxininic acid (14). These structures are based on the proposition that the functional groups present consist of two lactones, one ether and one hydroxyl group. The hydroxyl group is assumed to be tertiary, since it cannot be acetylated or oxidized, and it must be near the isopropenyl group, since it participates in bromination and is no longer present in the bromopicrotoxinins. The hydroxyl group could be located at C-6 or C-13, and the C-6 could be expected to bridge to the double bond during the bromination. In addition to this, the mechanism of the reverse aldol condensations yielding the alkaline cleavage products requires that the C-6 oxygen be not bound as a stable oxide bridge. Since none of the bromo-derivatives in this series undergo alkaline cleavage it is likely that this oxygen is the one involved in both reactions. Hence the structure of the bromopicrotoxininic acids would be



The lactone group present in these compounds is assigned as C-15; the free acid is assigned as C-14, since this is the carbon lost as CO_2 in the formation of picrotoxinide. Infrared data suggest that the lactone is six-membered and, that it is attached similarly to the transannular lactone in picrotoxinide. β-Bromopicrotoxininic acid has one secondary hydroxyl group, hence there are two possible structures, IX and X.

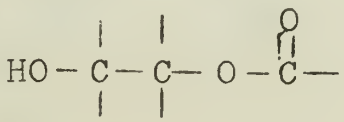


IX



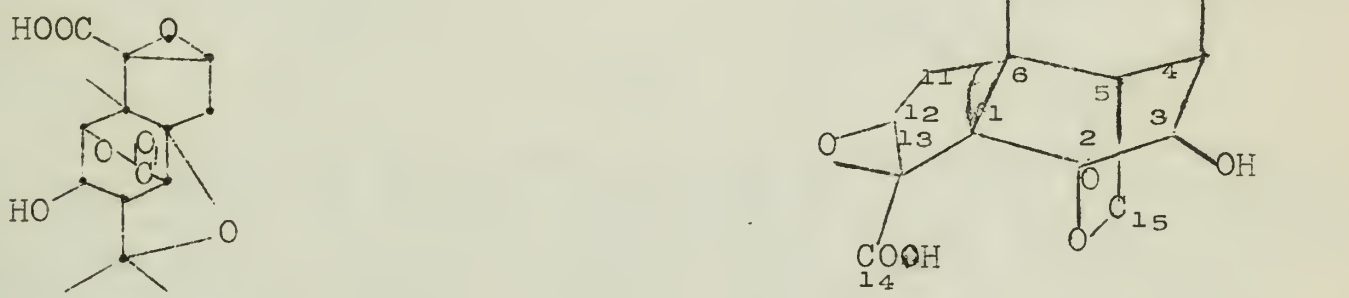
X

The structure IX is rejected for two reasons. It is badly strained. The stable oxide bridge blocks both pairs of vicinal oxygen atoms, which is inconsistent with the observation that hydrolysis of one lactone with dilute base results in a compound which readily reacts with periodate, thus requiring the system



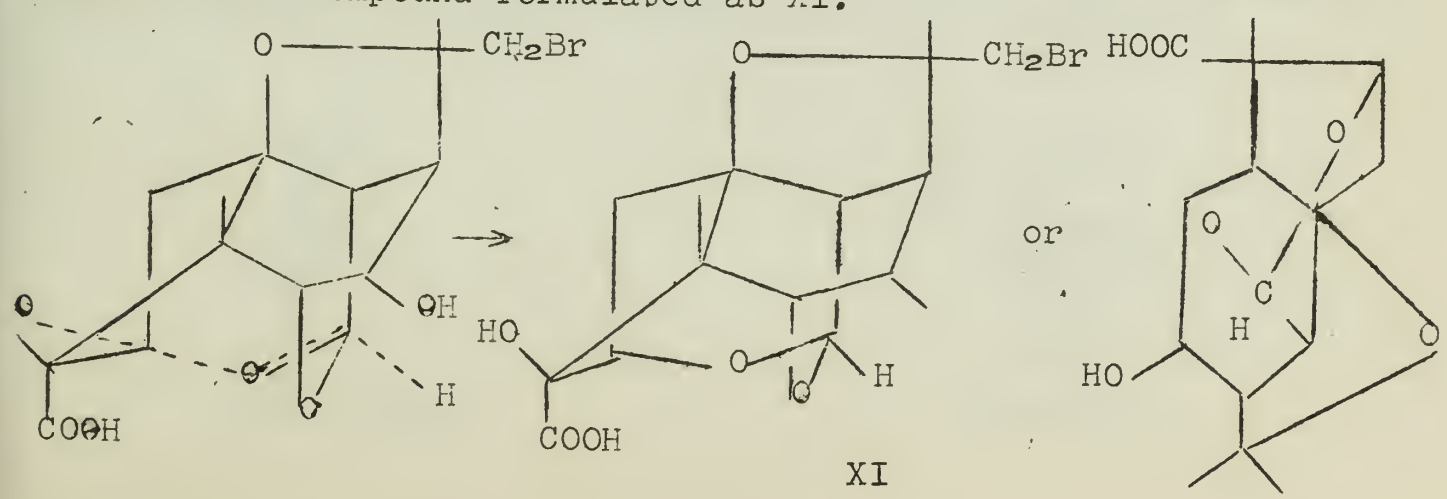
which would hydrolize readily to a free vicinal glycol. The formation of picrotoxinide is viewed as the thermal decomposition of a glycidic acid to a ketone followed by loss of water from the resulting β-hydroxyketone.

The Stereochemistry of β-Bromopicrotoxininic Acid: The above structure of β-bromopicrotoxininic acid is supported by the stereochemistry and reactions of β-bromopicrotoxininic acid. The C-3 hydroxyl had been shown to be <u>trans</u> to the isopropyl group in tetrahydrodesoxypicrotoxinide, and since the possibility of inversion is remote it has been assumed that the hydroxyl is <u>trans</u> to the β-bromoether. The transannular lactone must be <u>trans</u> to the β-bromoether (<u>cis</u> is sterically impossible) and the oxirane ring must be <u>cis</u> locked. The fact (to be discussed later) that this series of compounds forms a stable γ-lactone involving the C-2 and the C-14 oxygens establishes the structure of β-bromopicrotoxininic acid as shown in X.

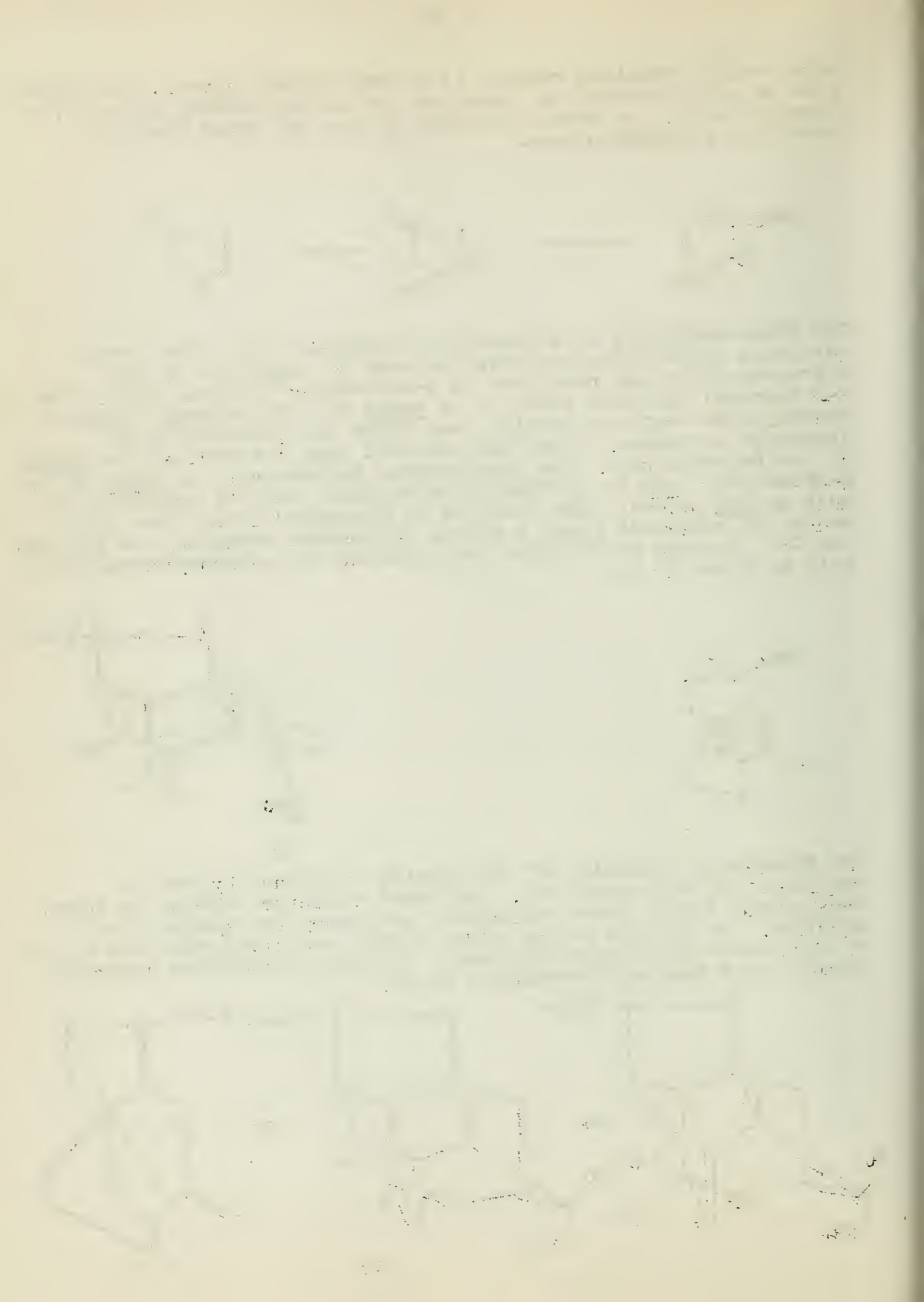


X

The remarkable stability of the epoxide to attack by acid is explained by this structure. The caged structure blocks the rearward attack (or at least solvation) necessary for epoxide ring opening. The lactone bridge which blocks backside attack can act as an intramolecular displacing agent. Lithium borohydride reduction results in a compound formulated as XI.

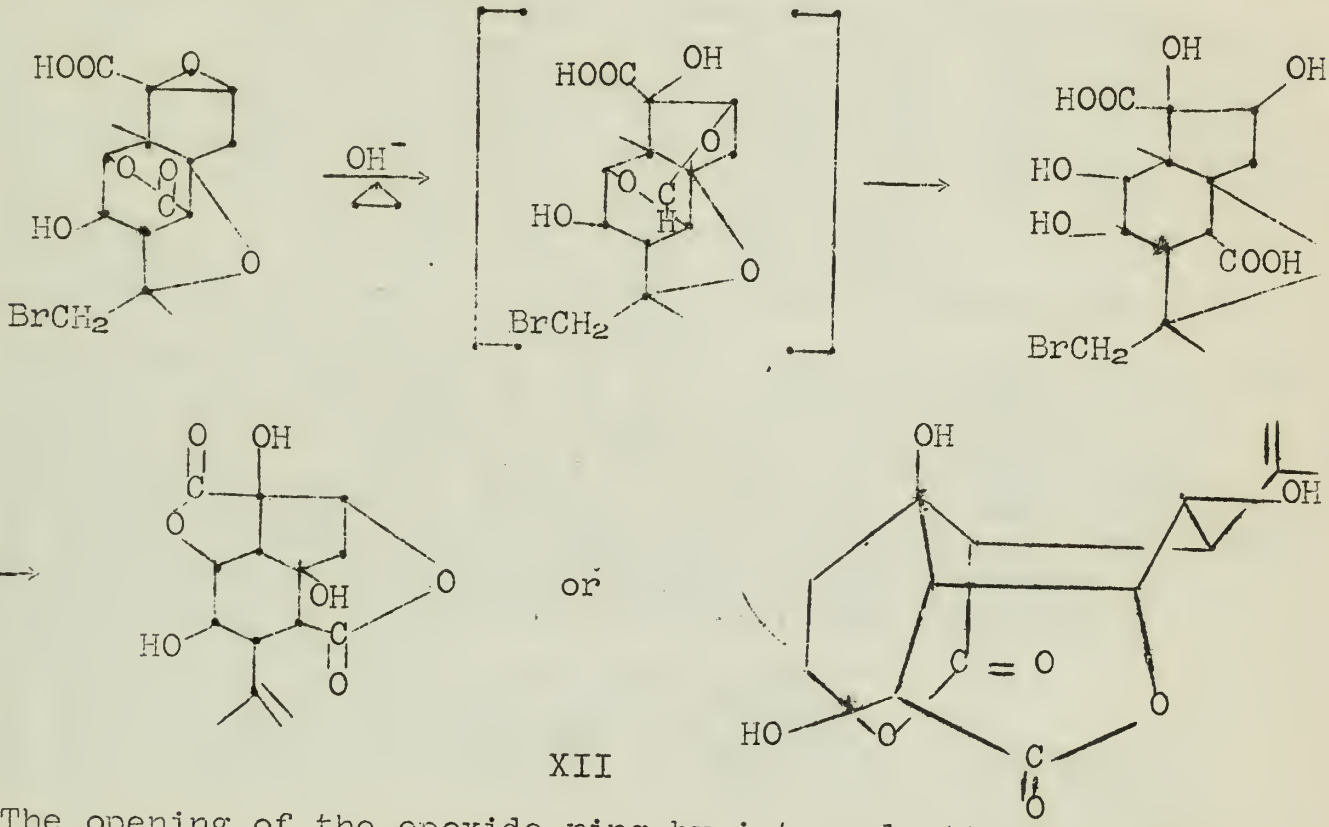


XI



The mechanism of this reaction has been postulated as shown.

The hydrolysis of β-bromopicrotoxininic acid provides a similar example. Hydrolysis of this compound followed by zinc-ammonium chloride debromination yields apopicrotoxininic dilactone ($C_{15}H_{18}O_7$) which is isomeric with β-picrotoxininic acid but is not acidic. Analogously to the above, the structure of this compound has been formulated as XII.

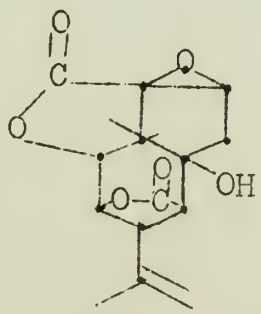


XII

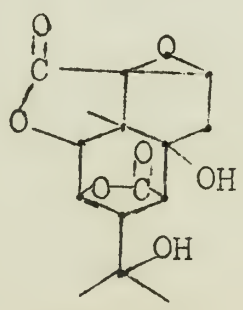
The opening of the epoxide ring by internal attack is taken as establishing the oxirane formulation and also the stereochemistry in this series. In a recent communication Conory has used the above mechanism to establish the structures of a series of lithium aluminum hydride reduction products obtained by the New Zealand group (15, 11). Robertson, et al., have an article on the lithium aluminum hydride reduction products in this series which is in press (16).

SUMMARY:

According to the best available evidence the structures of picrotoxinin and picrotin may be formulated as follows:



Picrotoxinin



Picrotin

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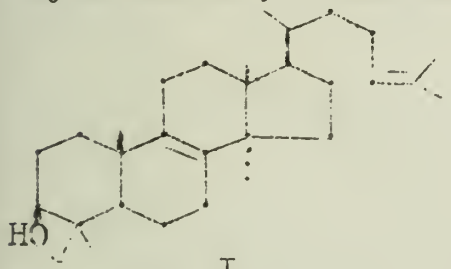
THE SYNTHESES OF LANOSTEROL, LANOSTENOL, Y-LANOSTEROL, AND AGNOSTEROL FROM CHOLESTEROL

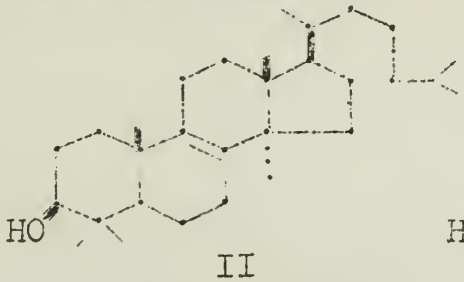
Reported by D. E. Frankhouser October 7, 1957

INTRODUCTION

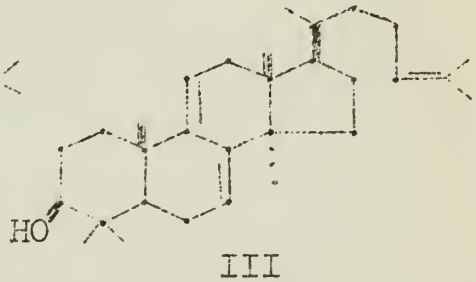
"Isocholesterol", which is isolated from sheeps' wool fat, is a mixture of four triterpenoids. The fraction consists of four alcohols: lanosterol (I), lanostenol (II), agnosterol (III), and Y-lanosterol (IV) (1). All of these alcohols are derivatives of the saturated hydrocarbon, lanostane (V), whose numbering is shown.



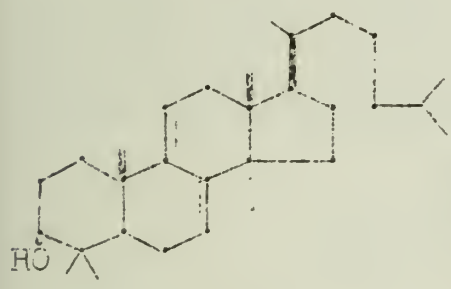
I



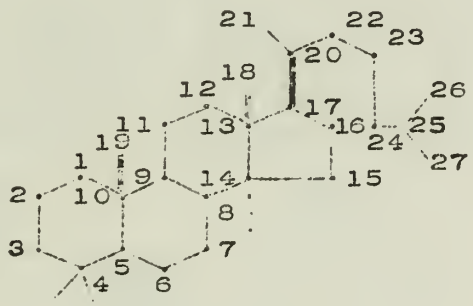
II



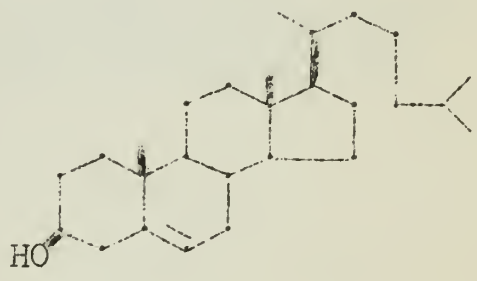
III



IV



V



VI

The constitution of the four triterpenoids has been established by degradation (2) and by X-ray crystallography (3). The relative and absolute stereochemistry were established by X-ray, chemical (4), biochemical (5), and molecular-rotation (6) evidence.

Cholesterol (VI), which has been previously synthesized (7), can be converted into each of the four components of the triterpenoid fraction of wool fat (8). A comparison of cholesterol (VI) with the four triterpenoids shows that the synthetic route to these products entails the following transformations.

A. Introduction of a gem-dimethyl group in ring A at C_4.
B. Introduction of a methyl group at C_{14}.
C. Elimination of a double bond at 5(6) position.
D. Introduction of double bonds at
   (1) 8(9) position (lanosterol and lanostenol).
   (2) 7(8) and 9(11) position (agnosterol and -lanosterol).
   (3) 24(25) position (lanosterol and agnosterol).

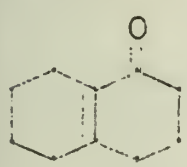
This seminar will present the synthesis of all four wool-fat triterpenoids. The structure proofs of these compounds and the synthesis of cholesterol will not be discussed because of lack of space.

I. SYNTHESIS OF LANOSTENOL AND γ-LANOSTEROL

Lanostenol and γ-lanosterol both have saturated side chains at C_{17}. Their preparation will be described first.

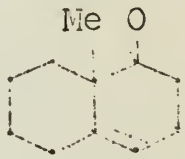
A. Introduction of gem-dimethyl group at C_4.

A technique for methylating the α-carbon atom of α,β-unsaturated ketones was developed by Birch (9). He reasoned that if compounds of type VII could be coverted into salts containing mesomeric anions of type VIII, then the action of methyl iodide on these salts could be expected to yield compounds of type IX.



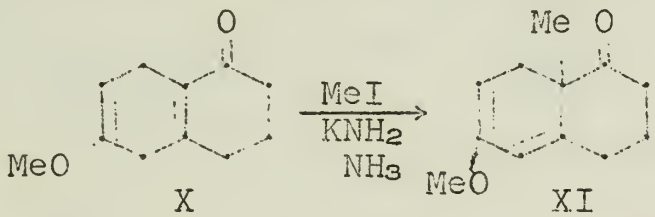
VII

VIII



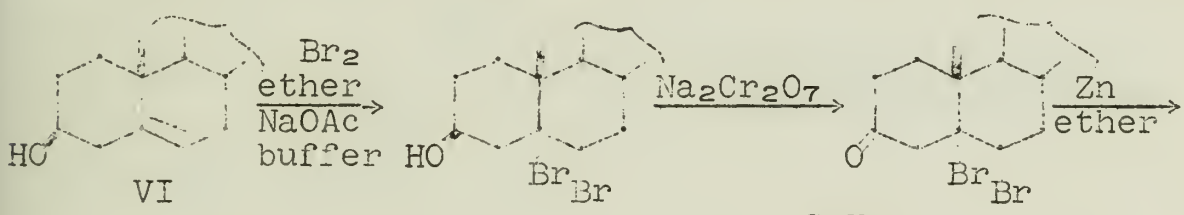
IX

The requisite salt (VIII) may be produced by the action of a suitable strong base, while in other cases an indirect route through the enol-ester may be needed. An example of this methylation was the successful conversion of X into XI by the action of methyl iodide and potassium amide in liquid ammonia.

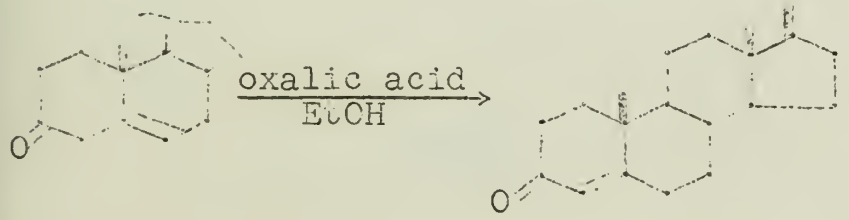


X XI

On this basis a suitable intermediate for the methylation would be 3-keto-cholest-4-en (XII) especially since convenient routes to this compound are available (10). This intermediate was prepared according to Fieser's scheme (11) starting with cholesterol (VI).



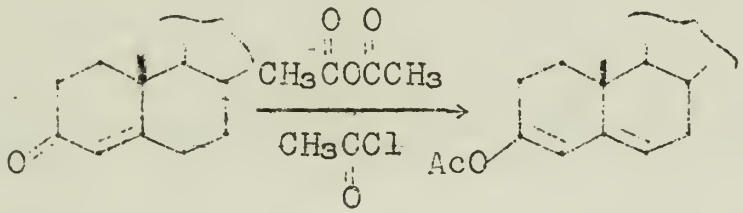
VI



XII

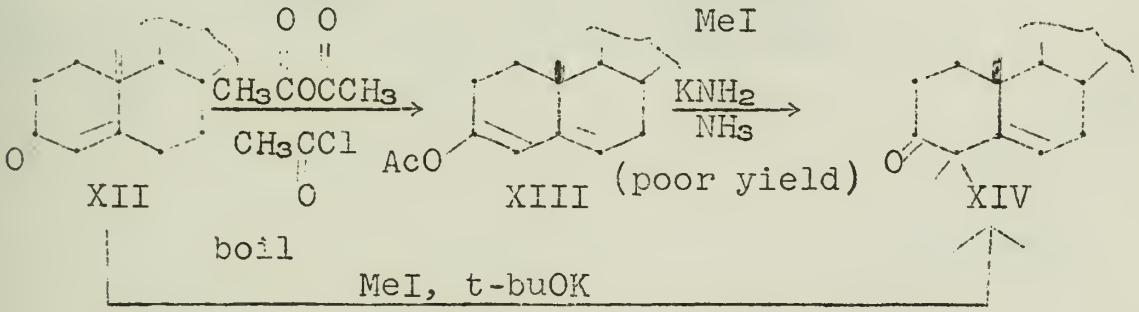
The oxidation of the hydroxyl group could also have been done by Oppenauer oxidation, but the method outlined in the scheme was quicker and was reported to give a more pure product.

It was thought that the methylation would best proceed by means of the enol-acetate. This was prepared according to Westphal (12), who had made the enol-acetates of progesterone and testosterone by boiling with a mixture of acetic anhydride and acetyl chloride.

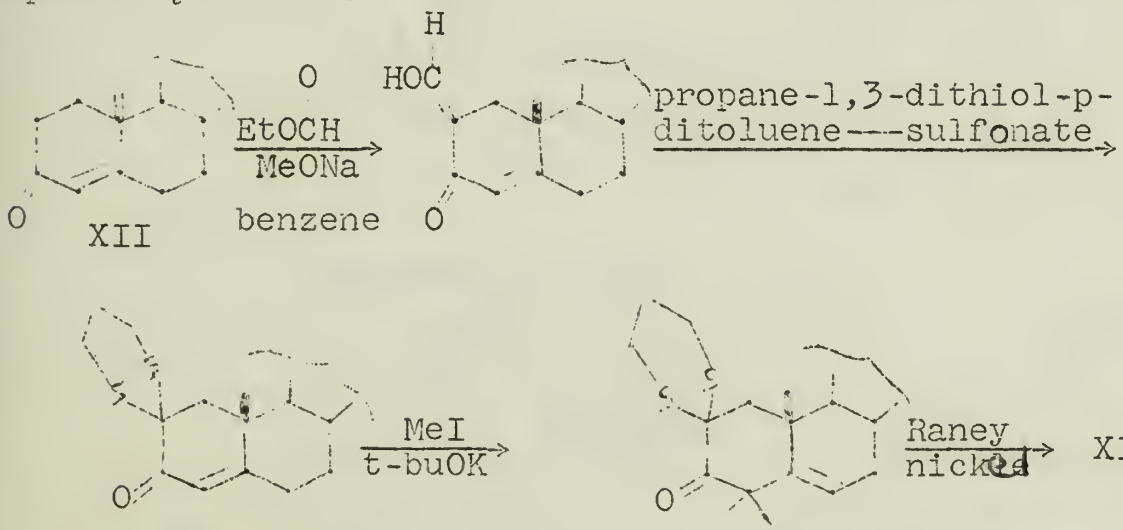


The product was definitely established by ultra-violet, bromination experiments, and reaction with maleic anhydride.

The 3-keto-cholest-4-en (XII) was transformed into the enol-acetate (XIII), which was then methylated with methyl iodide and potassium amide in liquid ammonia. The yield of 4,4-dimethyl-cholestenone, however, was poor. An alternative methylation with potassium t-butoxide and methyl iodide gave a superior yield. Later it was found that direct methylation of XII by potassium t-butoxide provided a more convenient synthesis.



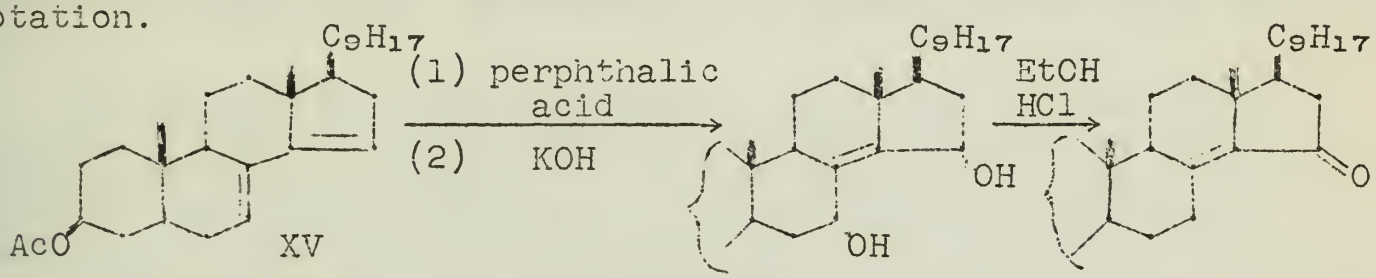
The proof of the structure of XIV was achieved by the following stepwise synthesis:



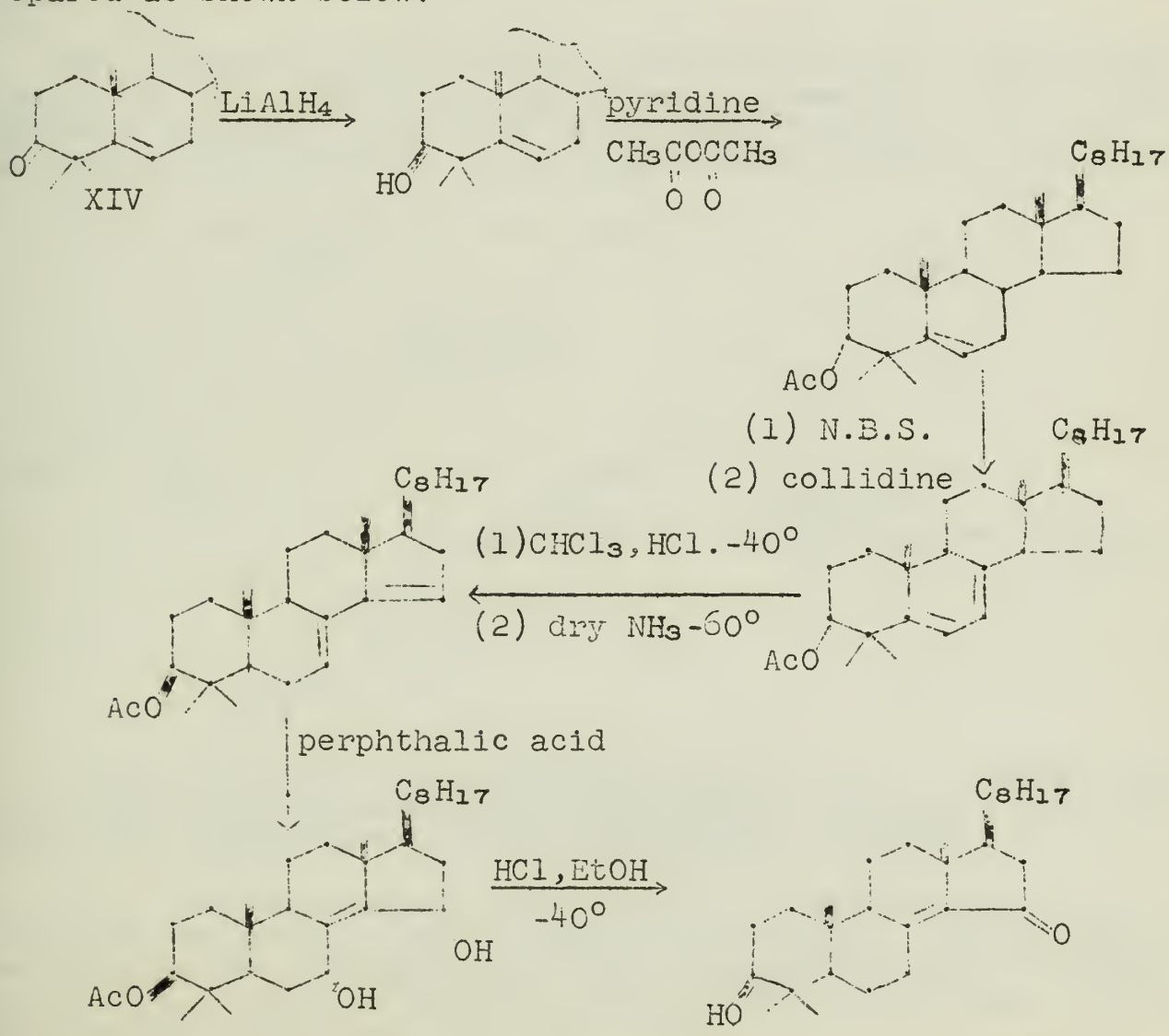
The products, XIV, of the two procedures were identical as shown by melting point, mixed melting point, and infra-red spectra. XIV showed no α,β-unsaturated carbonyl band.

B. Introduction of methyl group at C_{14} and rearrangement of double bond.

The methylation of C_{14} could conceivably be carried out by the method already used at C_4 if 15-keto-$\Delta^{8(14)}$-4,4-dimethyl-cholesterol (XVI) were the intermediate. Fortunately, compounds of the 15-keto-$\Delta^{8(14)}$ system had been prepared by Barton and Laws (13). They found that ergosta-7,14,22-triene-3β-yl acetate (XV) reacted with one mole of perphthalic acid to give a variety of products, chief of which was an unsaturated phthalate isolated as its sodium salt. After saponification, the resulting triol was dehydrated with ethanolic hydrochloric acid to give the desired 15-keto-$\Delta^{8(14)}$ compound, identified by melting point, mixed melting point, and rotation.



15-keto-$\Delta^{8(14)}$-4,4-dimethylcholesterol (XVI) was then prepared as shown below:



XVI

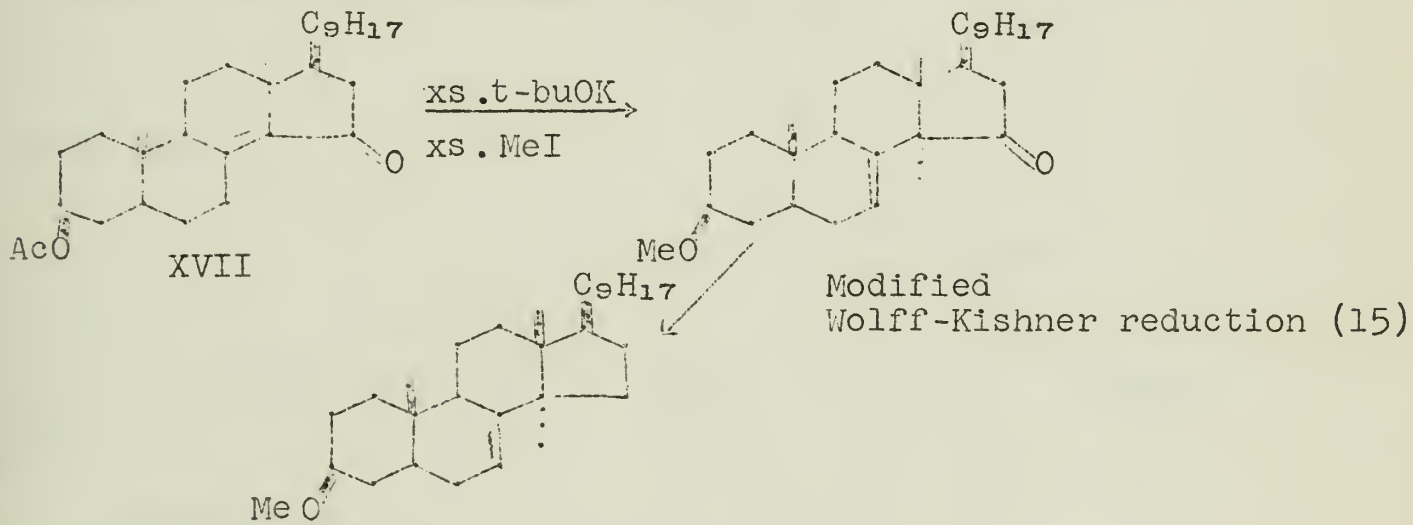
The isomerization of the double bond was performed in analogy to the work of Barton and Brooks (14), who prepared ergosterol B_3 from ergosterol as a part of their work with the hydrochloric acid induced isomerization of preformed diene systems.

While the preceding synthesis was being carried out, studies on the methylation of C_{14} of known 15-keto-$\Delta^{8(14)}$-compounds was attempted. Reaction of XVII with a slight excess of potassium t-butoxide and methyl iodide gave mainly unchanged starting material. A large excess of t-butoxide and methyl iodide gave the C_{14} methylated product in good yield. The product was identified by infra-red and analysis.

The 15-keto group in compounds of this type is sterically hindered. Thus, attempted reduction of this carbonyl by the ordinary Wolff-Kishner method resulted only in reduction to the alcohol. The simple precaution of using completely anhydrous conditions during the Wolff-Kishner reduction was found to be applicable to the reduction of sterically hindered carbonyl groups. This is the modified Wolff-Kishner method of Barton, Ives, and Thomas (15).

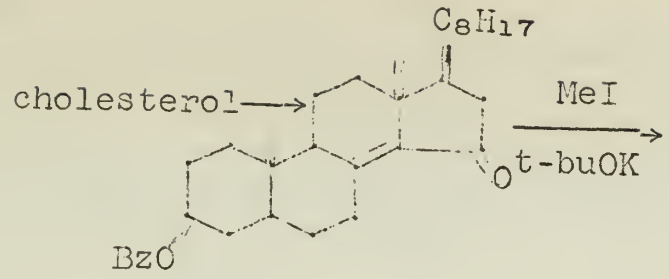
The 15-keto group of the C_{14} methylated model compound was then reduced by this modified method. The assignment of the nuclear ethylenic linkage to the 7(8) rather than the 8(9) position in these and related compounds is based on molecular rotation considerations.

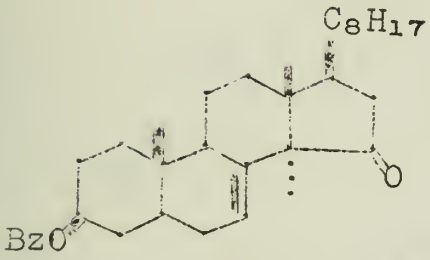
These reactions are shown below:



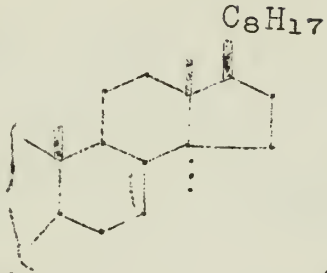
It will be noted that the methylation with t-butoxide and methyl iodide also results in methylation of the C_3 oxygen. This was avoided by methylation of the corresponding benzoate.

The previous synthesis showed that it would be possible to transform cholesterol into 14-methylcholestanol. Since lanostenol had already been degraded into this intermediate (16), it would provide a way for the inter-relation of cholesterol and lanostenol. The pertinent reactions are given below:

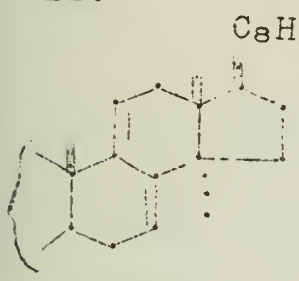




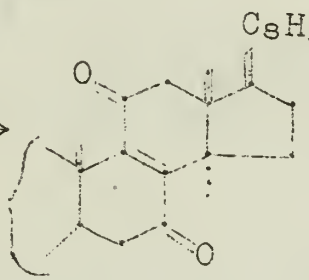
modified Wolff-Kishner(15)



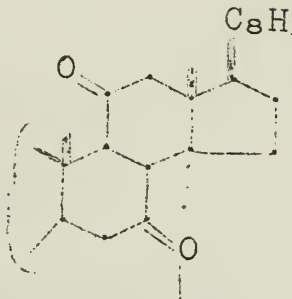
SeO_2



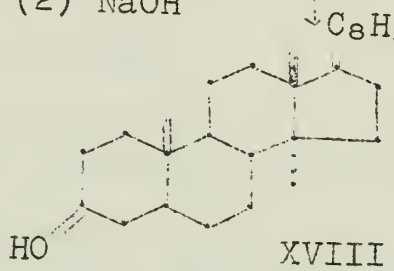
CrO_3



Zn
HAc

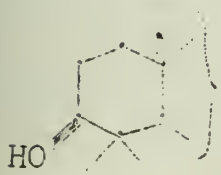


(1) Modified Wolff-Kishner (15)
(2) NaOH



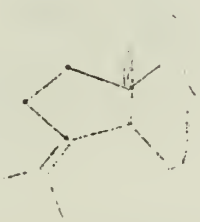
XVIII

lanostenol

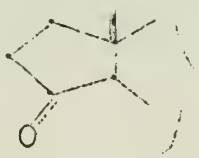


"lanostanol"

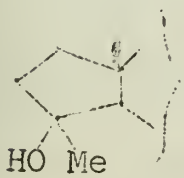
PCl_5



O_3
-60°

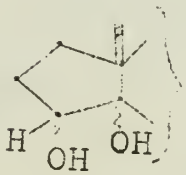


MeMgI

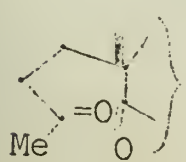


fullers earth

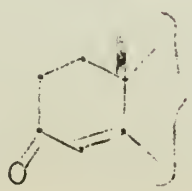
(1)OsO_4
(2)$LiAlH_4$



$Pb(OAc)_4$



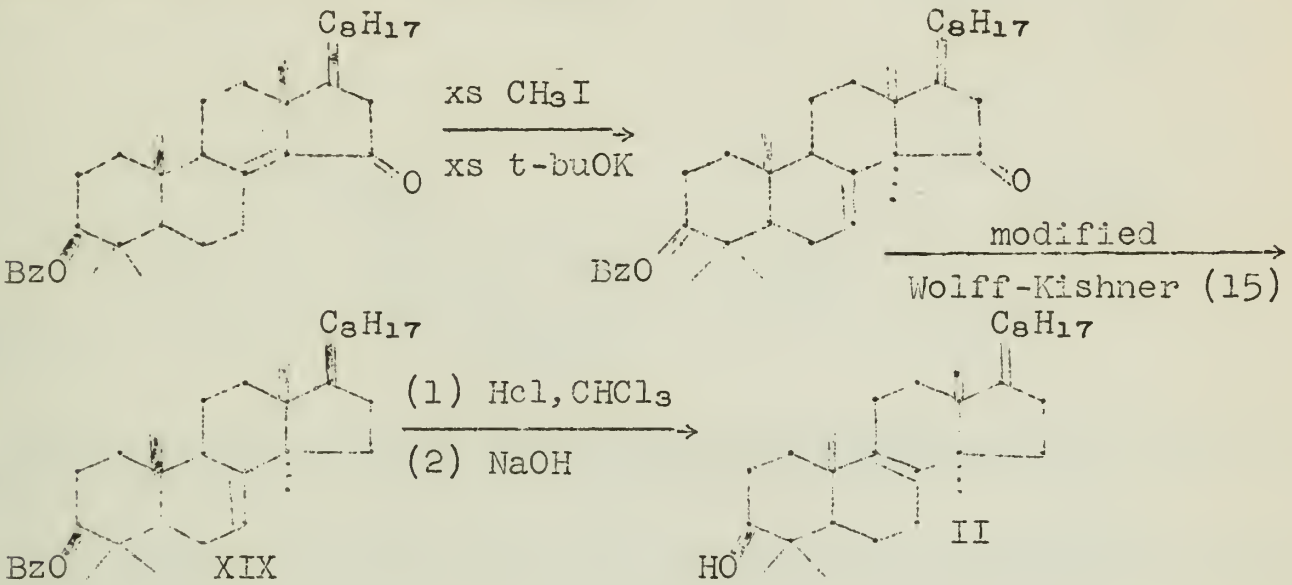
base cyclization



(1)Li, NH_3
(2)$LiAlH_4$

XVIII

With these preliminaries complete, the final steps from cholestero to lanostenol can be achieved. The isomerization of lanost-7-enol (XIX to lanost-8(9)-enol using hydrochloric acid in chloroform had already been reported (17). The structure of XIX was established by melting point, mixed melting point, and rotation. The lanostenol (II) was identified by comparing melting point, mixed melting point, and rotation with authentic lanostenol.

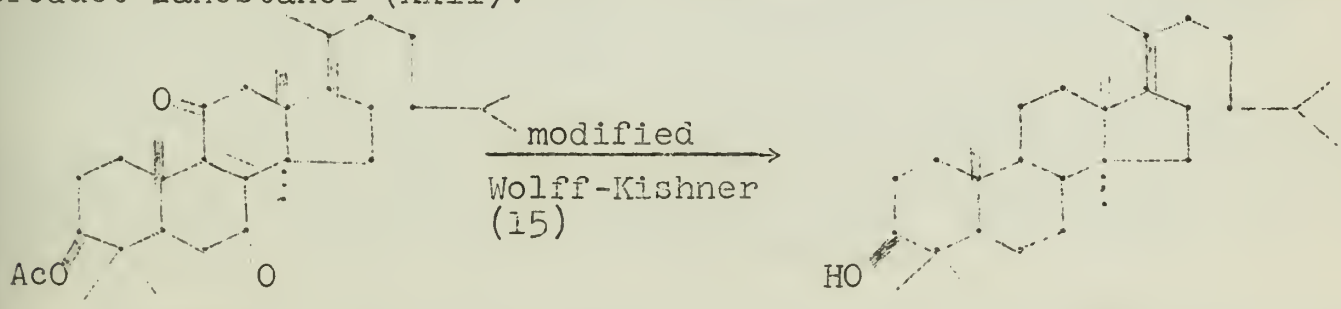


The oxidation of lanostenol (II) to 7-lanosterol (IV) had been reported on many previous occasions in work with the naturally occurring products. 8-lanosterol can be prepared by boiling lanostenol with selenium dioxide, N-bromosuccinimide, or chromic acid. (18)

II. SYNTHESIS OF AGNOSTEROL AND LANOSTEROL

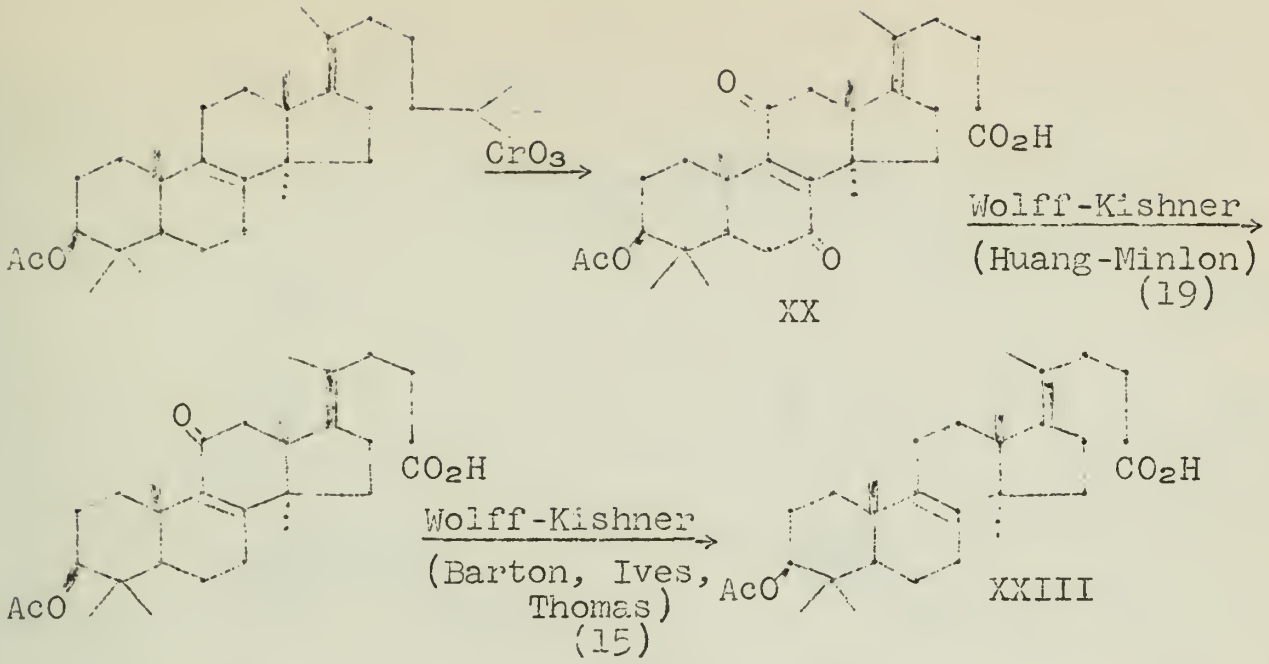
Both agnosterol (III) and lanosterol (I) have unsaturated C_{17} side chains, the double bond being located at the 24(25) position.

Lanostenyl acetate was oxidized with chromic oxide to give the diketone (XX), which is a known compound. The modified Wolff-Kishner method was used to attempt the reduction of the 7 and 11 ketone groups of a model compound, 7,11-diketolanostenyl acetate (XXI). This gave, instead of the expected product lanostenyl acetate, a fully saturated product lanostanol (XXII).



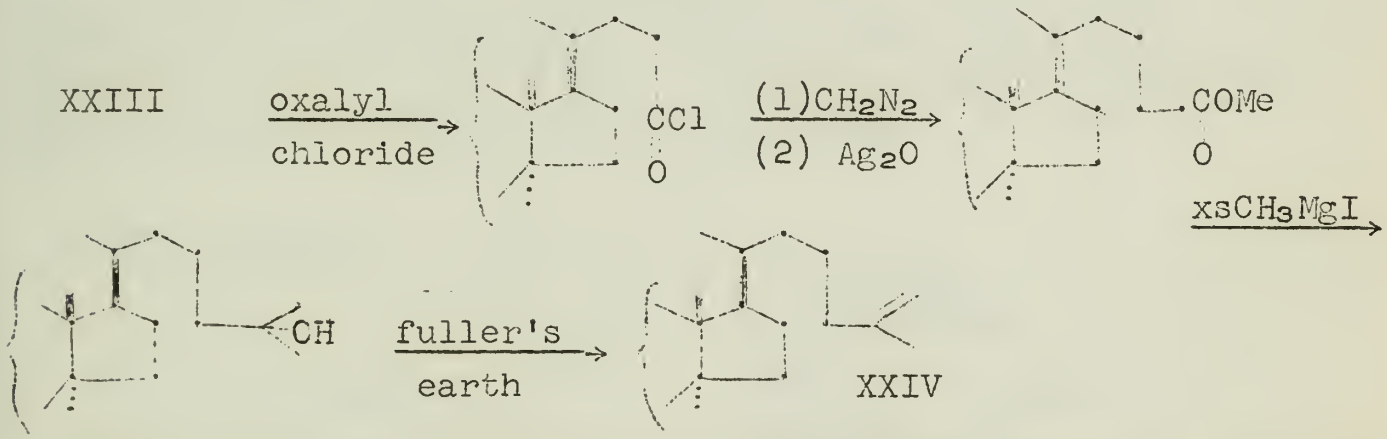
XXI XXII

A method for reducing keto groups at C_3, C_7, C_{12}, C_{17} and C_{20} by a Wolff-Kishner modification had been reported by Huang-Minlon (19). In all cases, however, the C_{11} keto group remained untouched. This method was used to reduce the C_7 keto group in the 7,11-diketo compound XX. The C_{11} carbonyl was then reduced by the Wolff-Kishner reduction of Barton, Ives, and Thomas (15) without touching the 8(9) double bond.



The structure of XXIII was proved by comparison with a product formed by ozonizing technical lanosteryl acetate.

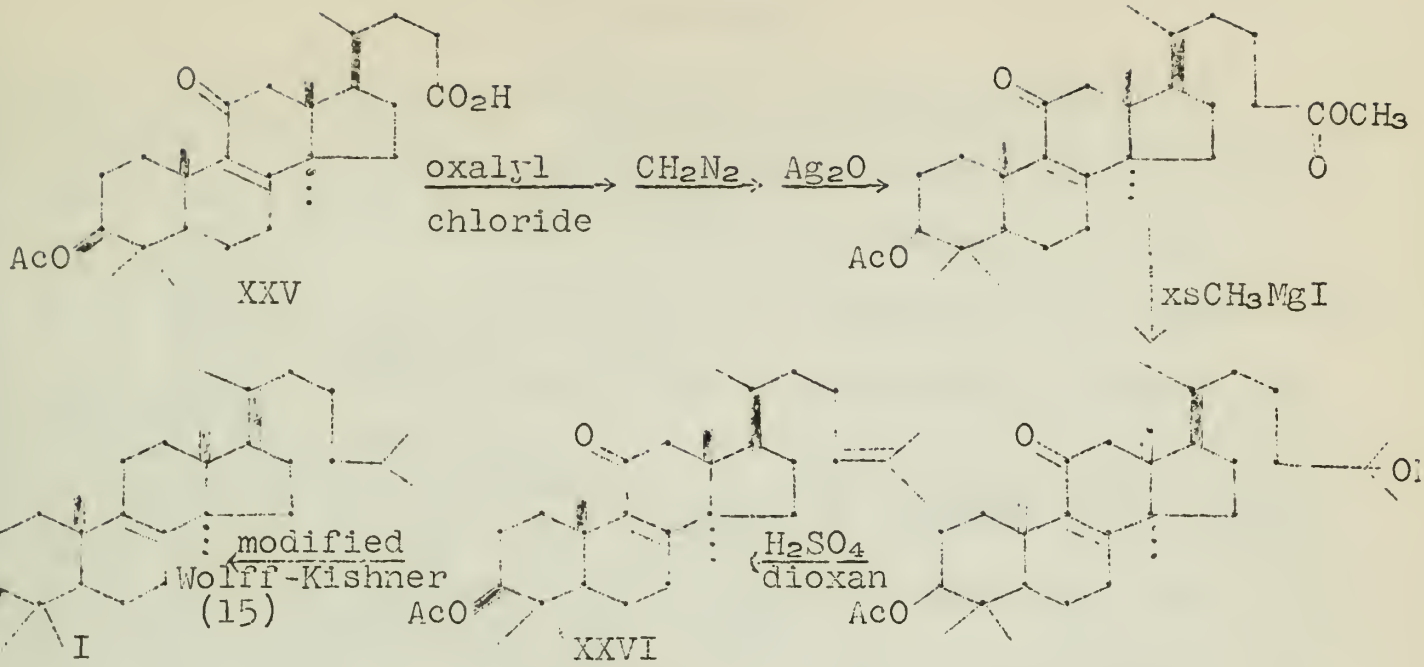
Rebuilding the side chain and introduction of the 24(25) double bond were performed by the following series of reactions:



Oxalyl chloride, instead of the more common reagents, was used to form the acid chloride because Wilds and Shunk (20) had employed it successfully with sensitive acids. Strong conditions might isomerize the 8(9) double bond. The product XXIV was shown to contain the 25(26) double bond by infra-red.

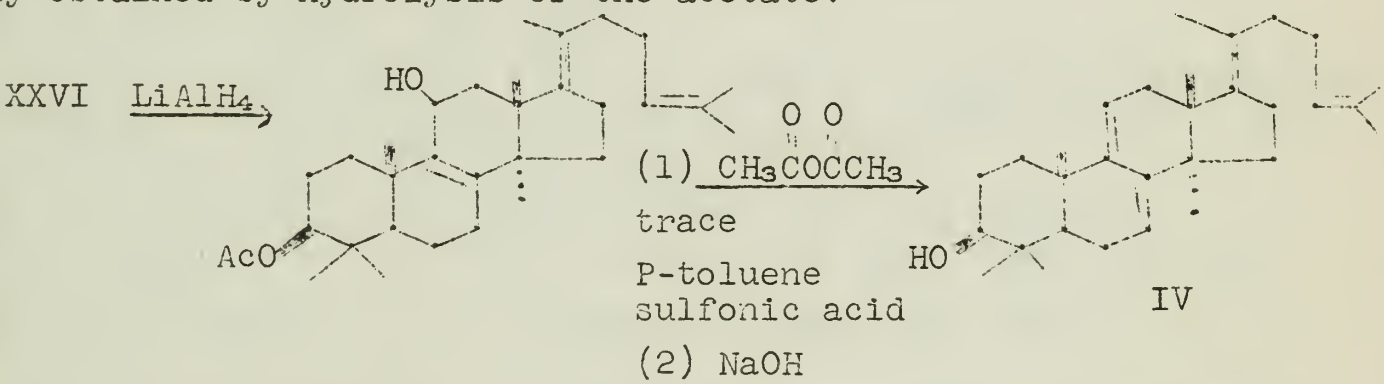
With the obtaining of the intermediate having the double bond at the 25(26) position, it was thought that it would be possible to define acid conditions which would allow isomerization of the 25(26) bond without isomerization of the 8(9) bond. This proved not to be possible and another route had to be found.

The difficulty was overcome by modifying the above procedure. Instead of reducing the C_{11} keto group, the 11-keto intermediate XXV was used directly in the synthesis. This served to prevent the isomerization of the 8(9) double bond since it remains α,β to the C_{11} carbonyl group.



Lanosterol (I) was definitely established as the product of the reaction by detailed comparison with authentic lanosterol.

The fourth and last wool fat triterpenoid, agnosterol (IV), was secured by use of an intermediate produced in the preceding scheme. This intermediate was 11-keto-3,24-dienyl acetate (XXVI), which was reduced with lithium aluminum hydride to the corresponding alcohol and then converted to agnosteryl acetate by heating with acetic anhydride and a trace of toluene-p-sulfonic acid. Agnosterol was easily obtained by hydrolysis of the acetate.



The melting point, rotation, and absorption intensity for the product were slightly higher than the recorded constants. (21) However, the value of γ at $\gamma_{max.}$ 243 mμ corresponds almost exactly to that recorded for authentic material. (22)

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THE STRUCTURE OF CERTAIN DELPHINIUM ALKALOIDS: LYCOCTONINE, DELPHELINE AND DELCOSINE

Reported by G. R. Bakker October 10, 1957

The alkaloids of the genera Aconitum and Delphinium have been receiving increased attention owing to genetic interest in their manner of occurrence in related plant species. In addition, certain widely occurring larkspurs are serious stock poisons. Yet no structures for the alkaloids found in these plants were known prior to 1954.

This seminar will cover three of the alkaloids related by the fact that the same basic structure has been proposed for them. The review of E. S. Stern presents a good background for all the known delphinium alkaloids, including those to be discussed (1).

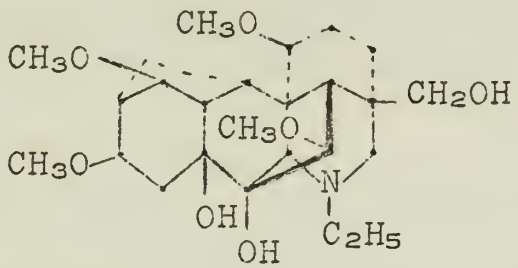
Lycoctonine was first isolated in 1865 (2) and has received intermittent attention since then (3,4,5). Most of the early work, however, was concerned with sources, isolation and preparation of the quaternary ammonium salts. Cause for this may be found in the difficulty in obtaining a pure product, failure of the Hofmann degradative scheme and the complex character of the skeleton itself. This lack of definitive structural work is also characteristic of much of the recent Russian investigations (6,7).

Lycoctonine is generally found esterified with some combination of acids from the following: anthranilic, succinic, methylsuccinic, acetic and benzoic acids. Hydrolysis can be performed either with acid or base (4,6,8). The manner of esterification has been reviewed and re-investigated by Cookson, Page and Trevett (9).

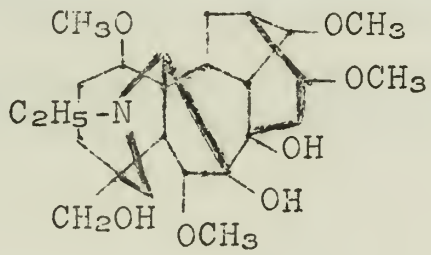
One of the first difficulties encountered in the study of the structure of lycoctonine was the determination of the correct empirical formula. Many formulae have been proposed (3,5,10); only recently has the correct formula been determined with any certainty as $C_{25}H_{41}O_7N$ (11). The oxygen substituents on the basic structure of lycoctonine have been known for some time to be four methoxyl and three hydroxyl groups (3). In contrast, the substitution on the nitrogen was the subject of some disagreement. Though a Herzig-Meyer N-alkyl determination gave ethyltrimethylammonium iodide (12), and acetaldehyde was formed when lycoctonine was treated with permanganate (5), the existence of an N-ethyl group was not proven unequivocally. The presence of an N-ethyl group was positively established in delsine, almost certainly identical with lycoctonine, by Abubakirov and Yunusov (13). They treated delsine with excess nitrous acid to obtain the N-nitroso compound and then obtained the free nor-delsine by decomposition with an alcoholic hydrochloric acid solution. The nor-base was then alkylated using ethyl iodide to obtain delsine again. Methylation with methyl iodide gave a different base.

With the knowledge given thus far, an expanded formula for lycoctonine was written: $C_{19}H_{21}(OH)_3(OCH_3)_4NC_2H_5$. This formula would demand a complicated basic skeleton of six or seven rings. The presence of unsaturation would decrease the number of rings required. However, lycoctonine and its simple transformation products are not hydrogenated in acid solution over Adams' catalyst (5). The ultraviolet spectrum shows only end absorption, which can be attributed to the basic nitrogen and to the hydroxyl and methoxyl groups (11). The

failure of fusion methods, dehydrogenations and the Hofmann degradation further complicated the problem. It was not until 1956 that a structure was proposed by Przybilska and Marion (14). Their analysis of X-ray data on the crystalline des-(oxymethylene)-lycoctonine hydriodide led them to suggest the following structure for lycoctonine:

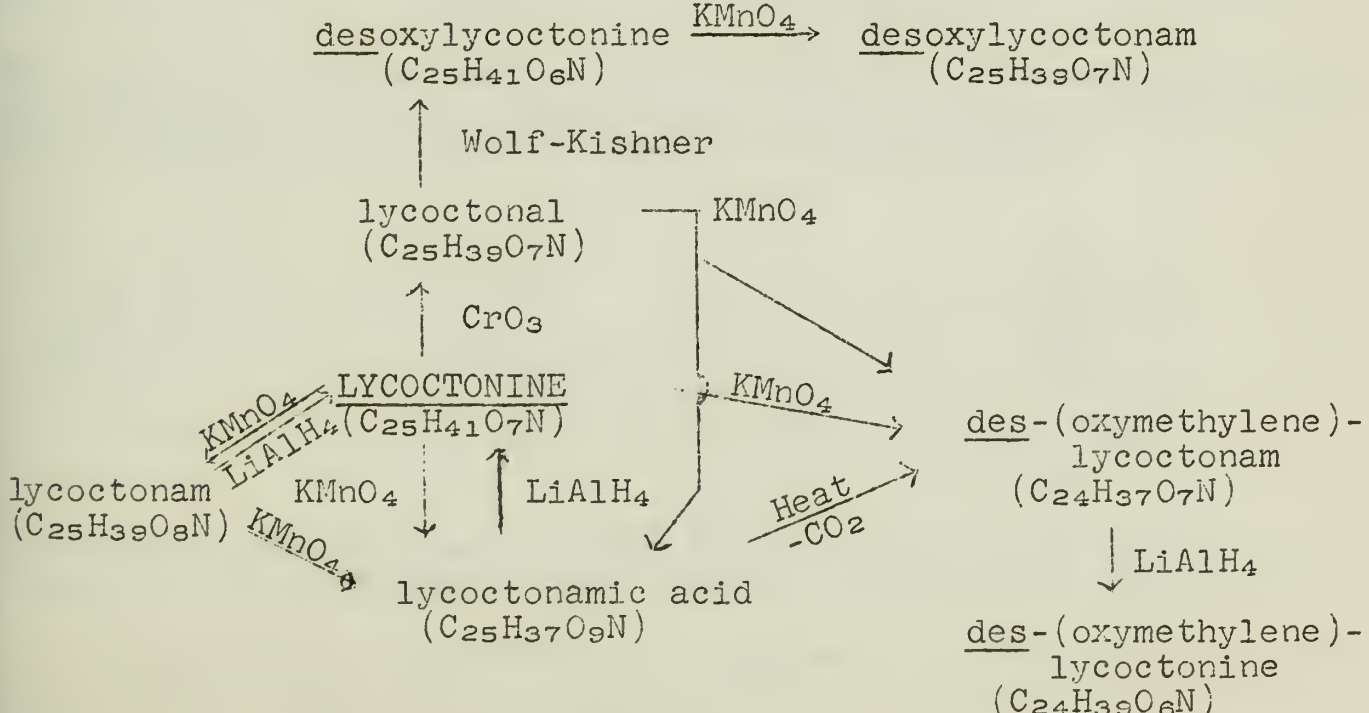


The only chemical assumptions reportedly used were the presence of an N-ethyl group and the position of the hydroxymethyl group. Another way of drawing this structure has been proposed in order that its relationship to the diterpene series may be seen (13).

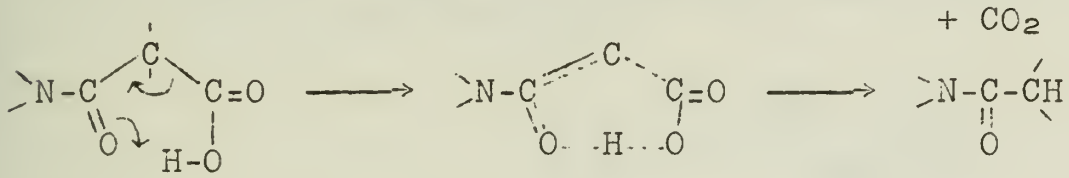


On the basis of this structure, most of the known chemistry of lycoctonine has been explained.

The oxidation of lycoctonine with permanganate and chromic anhydride gave a series of products which were characterized and can be represented by the following scheme (11):

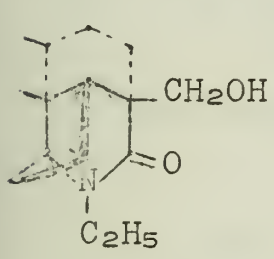


These reactions indicated the presence of a primary hydroxyl group and the presence of a methylene group next to the nitrogen. The position of the lactam absorption, ca. 1625 cm.$^{-1}$, indicated a six-membered (or larger) ring. The decarboxylation could have been attributed to α,β- or β,γ- unsaturation had there been evidence for a double bond. On this basis Edwards and Marion suggested an acid structure of the malonamic type unable to assume the planar transition state (11). This would explain the 200° decarboxylation temperature. (Usually 160° or less for malonamic acids.)

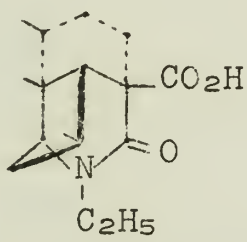


This suggestion was further confirmed by comparison of the pK's, infrared spectra and methyl esters of lycoctonamic acid and N-(α-carboxybutyryl)-piperidine. The tertiary nature of the carbon α to the carboxyl group was suggested by the very slow reaction of the methyl ester with bromine in carbon tetrachloride.

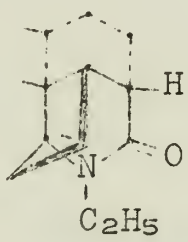
These facts can be accommodated by the lycoctonine structure given, and the partial formulae of the oxidation products can be written as follows (16):



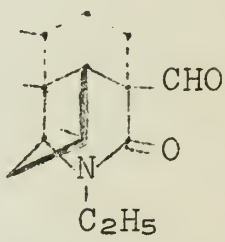
lycoctonam



lycoctonamic acid

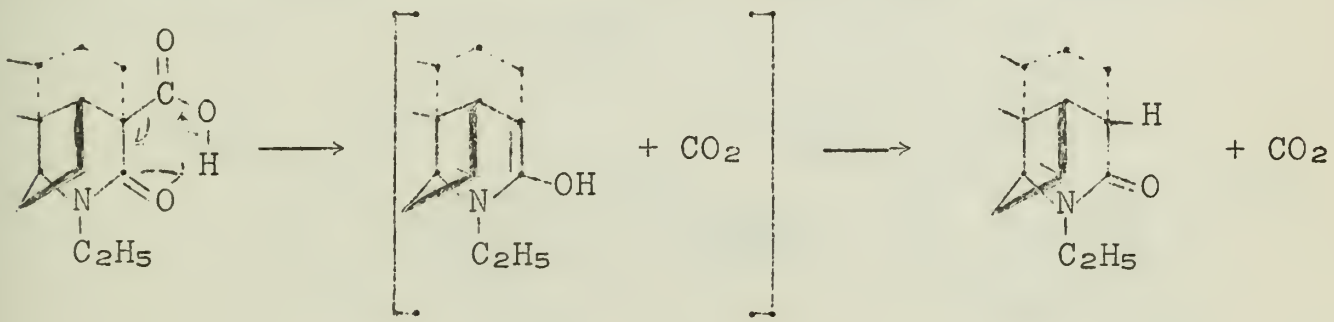


des-(oxymethylene)-lycoctonam



lycoctonal

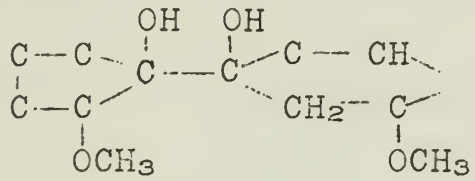
The transition state for the decarboxylation of lycoctonamic acid and the transient enol intermediate would involve a double bond at the bridgehead of an azabicyclo[3.3.1]nonane system.



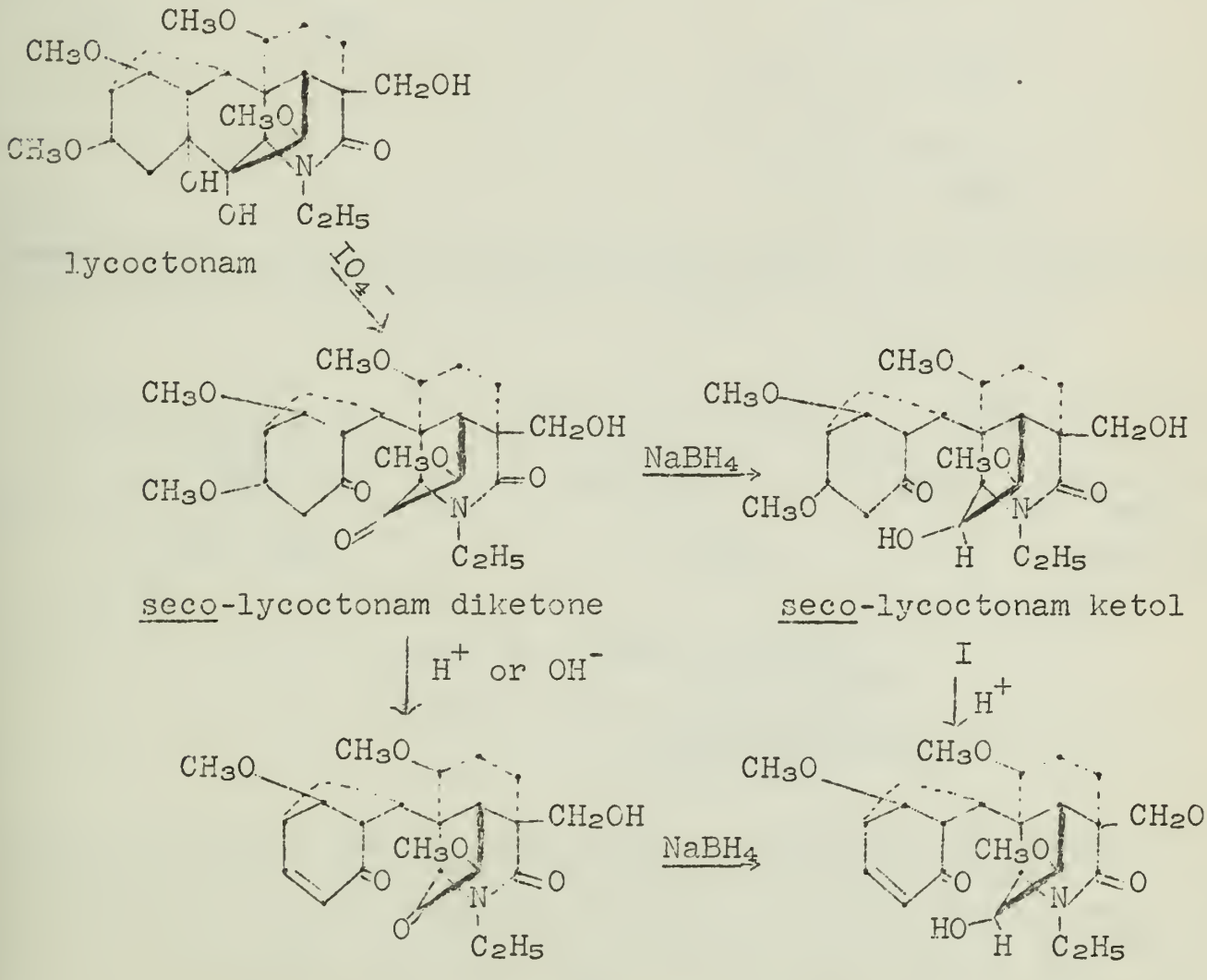
It has been shown, however, that Bredt's rule can be broken for transient intermediates in the bicyclo[3.3.1]nonane series (17).

Considerable information was derived from the periodate oxidation of the glycol (18). From lycoctonam a diketone was obtained which had two bands in the infrared, at 1766 and 1713 cm.$^{-1}$, indicative of a 5-membered ring ketone (carbonyl 1) and a 6- or more membered ring or straight chain ketone (carbonyl 2). Carbonyl 1 is readily reduced by sodium borohydride while carbonyl 2 is not. The

sodium borohydride reduction also destroys the ability of the diketone to reduce easily Tollens' reagent and Fehling's solution. This ready oxidation of carbonyl 1 was postulated as being due to the presence of an α-methoxyl group. Both the diketone and the ketol from the sodium borohydride reduction are sensitive to acid and base, losing the elements of methanol to give α,β-unsaturated ketones. β-Methoxy ketones are known to undergo this easy elimination; therefore, it was suggested that there was a methoxyl group β to carbonyl 2. The infrared and ultraviolet spectra are in accord with this interpretation. Thus, the following fragment was known to be part of the lycoctonine structure:



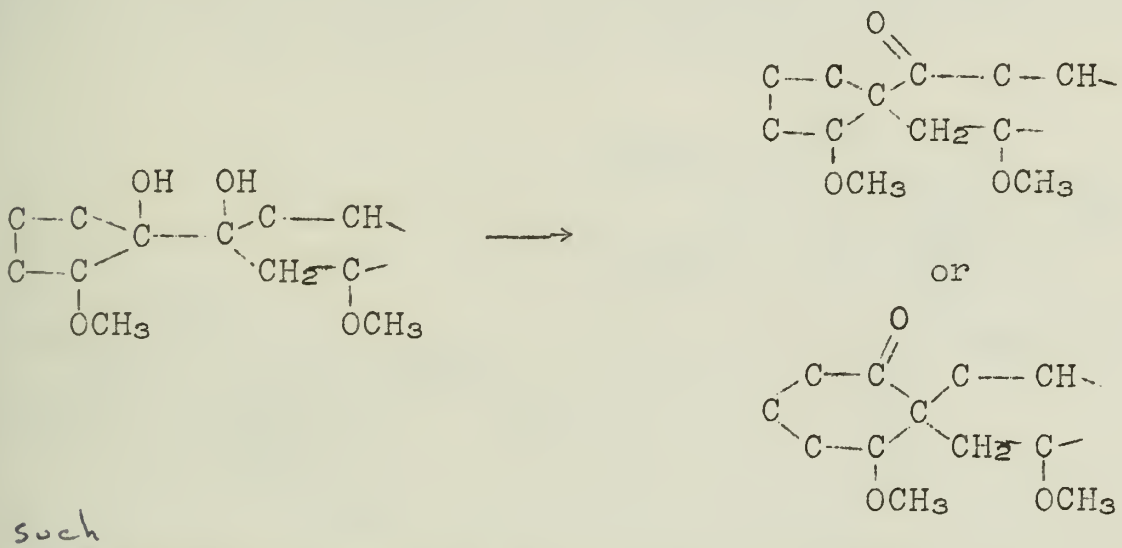
The reactions described above may be written using the known structure and it can be seen that the vicinal glycol fragment is present (16).



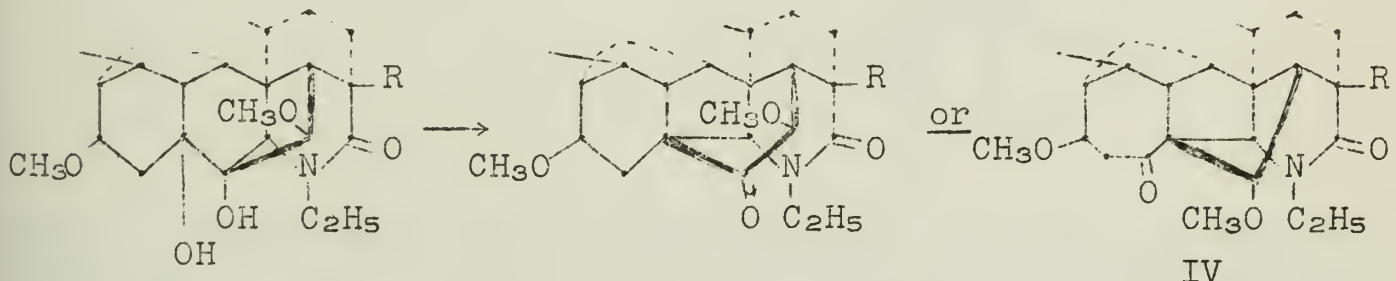
II

The acetylation reactions of lycoctonine and its derivatives can also be interpreted in terms of the X-ray determined structure. The action of acetic anhydride in pyridine on lycoctonam gave a

mono-acetate in which the primary alcohol was assumed to be acetylated The use of acetyl chloride on lycoctonam, however, led to a product which was named anhydrolycoctonam mono-acetate (11). Des-(oxymethylene)-lycoctonam gave anhydro-des-(oxymethylene)-lycoctonam upon treatment with acetyl chloride, as well as a mono-acetate, which upon heating lost acetic acid to give the anhydro product. At first this was thought to be a normal dehydration reaction of a tertiary-secondary glycol (19). However, the inertness of the vicinal hydroxyl groups to Oppenauer, permanganate and chromic acid oxidations suggested that both hydroxyl groups were tertiary. This was proven by the periodate cleavage of the glycol; accordingly, Edwards and Marion suggested that a pinacol rearrangement had taken place (18).



such
~~These~~ possibilities can be written in terms of the known structure and the more probably correct one chosen (16).



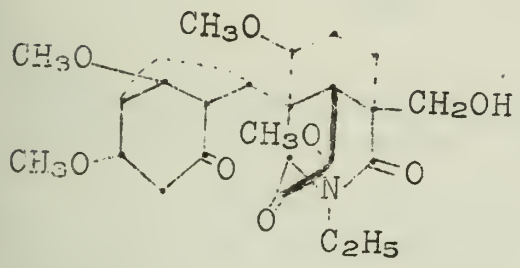
IV

IIIa, R = CH_2OH; anhydro-lycoctonam

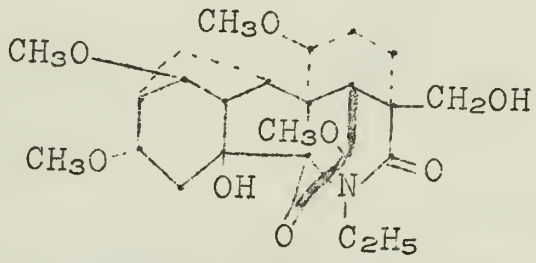
IIIb, R = H; anhydro-des-(oxymethylene)-lycoctonam

These structures are the only ones permitted by the geometry of the molecule, and of these two, IV can be eliminated since no α,β-unsaturated ketone was observed when the anhydro compound was treated with acid or base. The β-methoxy ketone of IV could be expected to lose the elements of methanol under such conditions. The interesting fact that anhydrolycoctonam (IIIa) is stable to hot dilute alkali whereas the analogous anhydro-des-(oxymethylene)-lycoctonam (IIIb) is not, can also be explained on the basis of the known structure (16). The reaction must be an epimerization at the carbon α to the carbonyl group. The nearly identical infrared spectrum of the product confirms this. With the bulk of the hydroxymethyl group gone, the carbon bearing the α-methoxyl group can now be epimerized.

When seco-lycoctonam diketone (V) was adsorbed on weakly acidic alumina or was treated with sodium bicarbonate, a compound was obtained with the same empirical formula but with carbonyl 2 replaced with a hydroxyl group and the absorption peak of carbonyl 1 shifted downward (18). The reaction was reversible since $NaBH_4$ treatment or catalytic reduction of this "iso" compound produced the seco-lycoctonam ketol (I), and strong alkali produced desmethanol-seco-lycoctonam diketone (II). The possibility of this reaction being a β-diketone going to a stable enol was easily discounted. There still remained two possibilities neither of which could be proven to be the correct one: a ketone going to an unsaturated alcohol, or an internal aldol condensation. Here the known structure helped to decide which was correct, for reasonable structures could only be written for the internal aldol condensation.

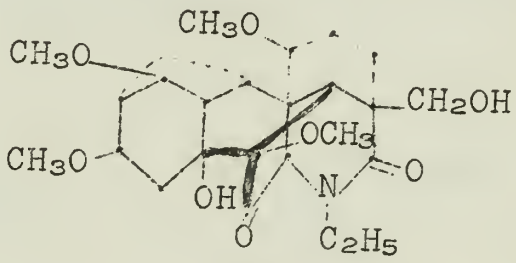


V



VI

or

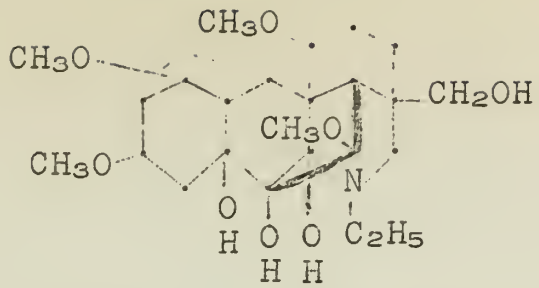


VII

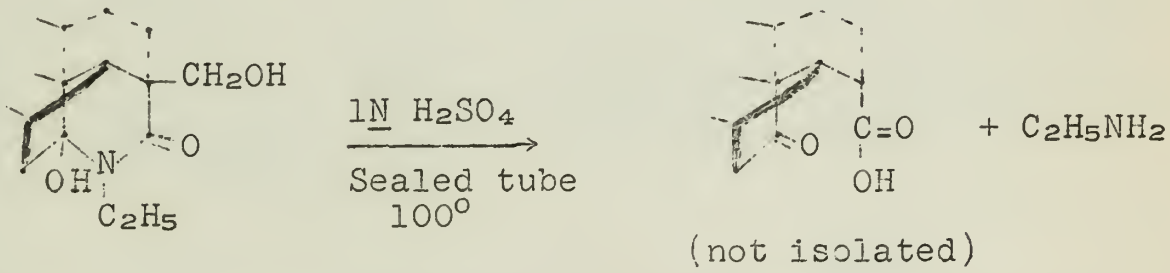
Since to obtain structure VI the requisite enolization of the ketone would place a double bond in the bridgehead of an azabicyclo[3.2.1]-nonane this product would not be obtained. Therefore structure VII is the most probable for the "iso" compound.

The action of hot dilute acid on the "iso" compound produced two new compounds, one of which appeared to have acquired again the lycoctonine structure with an additional ether linkage (16). Active investigation is proceeding on these compounds to determine the validity of the suggested structures.

Another compound, hydroxylycoctonine, has been studied in the light of the now known structure of lycoctonine (16). This was prepared by treating lycoctonine with fresh silver oxide in aqueous methanol (11). The pK of hydroxylycoctonine in aqueous methanol was 5.6, 3.2 units lower than that of lycoctonine, indicating a change in the vicinity of the nitrogen. Resistance to further oxidation, lack of carbonyl absorption in the infrared, and failure to undergo dehydration led Edwards, Marion and Stewart to postulate the following carbinolamine structure for hydroxylycoctonine:

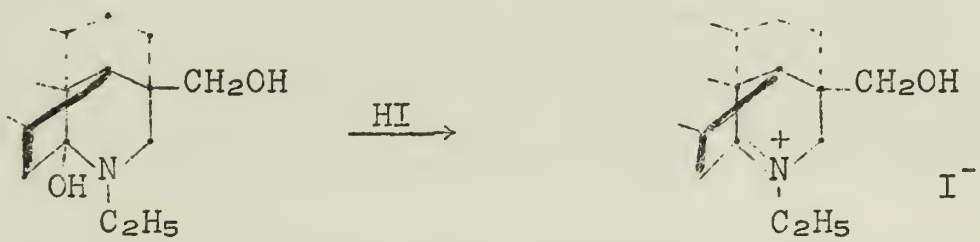


Hydroxylycoctonine undergoes a permanganate oxidation to products analogous to those obtained from lycoctonine (20). The hydrolysis of hydroxylycoctonam by 1N sulfuric acid in a sealed tube produced ethyl amine which was characterized as its picrate.



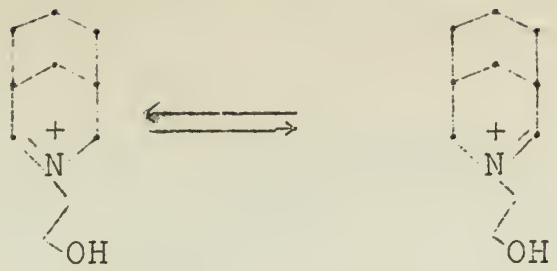
This hydrolysis was the reaction which established with certainty the presence of an N-ethyl group in lycoctonine.

In clear violation of Bredt's rule, hydroxylycoctonine appears to form anhydronium salts which precipitate out of solution (21). Elemental analysis and the infrared spectrum verify the formation of the anhydronium salt.



Though the structure of hydroxylycoctonine which has been presented has a vicinal triol, this has not been apparent from cleavage reactions. Hydroxylycoctonine consumes only one mole of periodate or lead tetraacetate. Hydroxylycoctonam reacts with only one mole of lead tetraacetate, and the products from this and succeeding reactions appear to be analogous to the products obtained from the same oxidation of lycoctonam (16).

When hydroxylycoctonine was heated in 20% ethanol at steam-bath temperatures for eight hours and then allowed to remain overnight at room temperature, a reaction took place which gave at least four products: lycoctonine, des-(oxymethylene)-lycoctonine, formaldehyde and acetaldehyde. The mechanism suggested demands isomerization of the double bond of the anhydronium base formed from hydroxylycoctonine (16) and subsequent reduction by the formaldehyde or carbinolamine present. That such an isomerization can occur is questionable. Conrow has shown, by the lack of incorporation of deuterium, that in a very similar model system the following isomerization does not take place appreciably within eight hours (22):



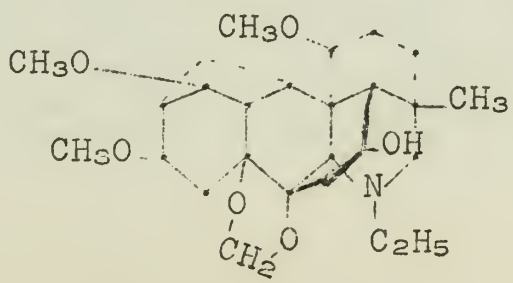
Unless some other explanation can be found for the formation of the observed products, this and the periodate cleavage cast some doubt on the proposed structure of hydroxylycoctonine.

There is another fact which cannot be explained on the basis of the proposed structures. Methyl hydroxylycoctonamate is much more resistant to hydrolysis than methyl lycoctonamate. The distance between the carboxyl group and the new hydroxyl group would prevent any possible interaction. Methyl hydroxylycoctonamate may be diagrammed in the following ways:

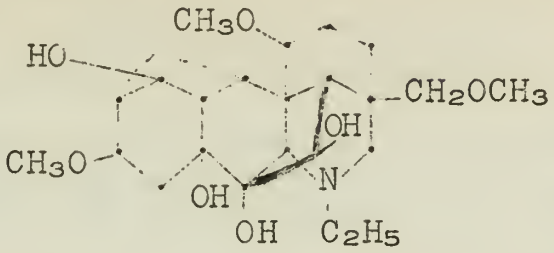
There remains yet the interpretation of the degradation product obtained when lycoctonam and anhydrolycoctonam are treated vigorously with strong acid (23). It has been suggested that this product, lycoctamone, arose from the hydrolysis of a methoxyl to a tertiary hydroxyl group and the elimination of a second methoxyl group as methanol to give an α,β-unsaturated ketone. These suggestions are untenable in the light of the known structure of lycoctonam and anhydrolycoctonam (16).

There are at present two other Delphinium alkaloids for which the same basic structure has been postulated, delpheline and delcosine.

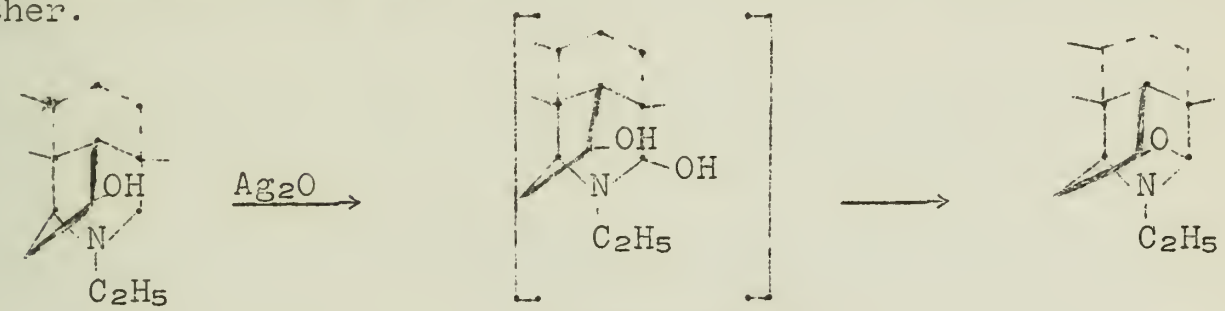
The chemistry and structure of delpheline have been investigated largely by Cookson and Trevett (24,25). The empirical formula had been found to be $C_{25}H_{39}O_6N$. The substituents are three methoxyl groups, one hydroxyl group and two ethereal oxygen functions (26). Oxidations, acetylation, periodate treatment, and acid and base treatment gave many facts, some very similar to those obtained from lycoctonine. Most of these reactions have been explained in the light of the following structure suggested for delpheline:



Delcosine has also been studied for some time (12,27,28). Its chemistry can be explained by use of the following structure (29):



An interesting variation observed with delcosine is the formation, upon treatment with silver oxide, of a cyclic carbinolamine internal ether.



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MECHANISMS OF THE REACTIONS OF ORGANOMERCURIALS

Alex. D. Argoudelis October 14, 1957

INTRODUCTION

Organomercurials have been used extensively as convenient materials for the study of the mechanisms of different chemical reactions.

The easy decomposition, thermally or by irradiation, to give free radicals has been proved to be a useful tool for the study of the behavior of free radicals.

On the other hand the ease with which organomercurials enter into displacement reactions and their electrophilic character make them convenient means for the study of ionic reactions.

The subject of this seminar is the study of both free radical and ionic reaction mechanisms of these compounds.

THERMAL AND PHOTOCHEMICAL REACTIONS OF ORGANOMERCURIALS

Since the covalent bonds of organic compounds of heavy metals such as lead, tin, and mercury are all relatively weak it is expected that free radicals should be formed by thermal decomposition (1).

The thermal decomposition of mercury dimethyl was studied by Gowenlock, Polanyi and Warhurst (2). The reaction was followed by analysis of the mercury produced as well as by gas analysis for methane, ethane, ethylene, etc.

The first order rate constants obtained were shown to be independent of the partial pressure of mercury dimethyl and of contact time.

They assumed A, the Arrhenius frequency factor, equal to 1.0×10^{13}. The calculated activation energies which they identify with reaction (I-1), a simple unimolecular change, were 51.5 and 49.5 kcal in experiments at two different pressures.

The mechanism suggested is

$$Hg(CH_3)_2 \rightarrow \cdot CH_3 + HgCH_3 \quad (1)$$

$$HgCH_3 \rightarrow Hg + \cdot CH_3 \quad (2)$$

$$2 \cdot CH_3 \rightarrow CH_3CH_3 \quad (3) \qquad (I)$$

$$\cdot CH_3 + Hg(CH_3)_2 \rightarrow CH_4 + \cdot CH_2HGCH_3 \quad (4)$$

$$\cdot CH_3 + \cdot CH_2HgCH_3 \rightarrow CH_3CH_2HgCH_3 \quad (5)$$

$$2 \cdot CH_2HgCH_3 \rightarrow (CH_3HgCH_2)_2 \quad (6)$$

From the products obtained they concluded that (I-6) is negligible.

In the presence of hydrogen the additional reactions (II) take place.

$$\cdot CH_3 + H_2 \rightarrow CH_4 + H\cdot$$
$$H\cdot + CH_3HgCH_3 \rightarrow CH_4 + CH_3Hg \qquad \text{(II)}$$

etc.

Moore and Taylor (3) found no appreciable thermal decomposition of mercury diethyl up to 250°C.

Ivin and Steacie (4) found that the decomposition of mercury diethyl vapor at 100°, 150° and 200° is largely heterogeneous and experiments in a cell packed with tubing, gave rates higher by a factor of from 2 to 5. No mechanism was suggested.

Cowenlock, Polanyi and Warhurst (2) investigated the decomposition of mercury diethyl in a manner similar to that of mercury dimethyl. From the product obtained and the found first order rate constants, they concluded that the mechanism is (III).

$$Hg(C_2H_5)_2 \rightarrow C_2H_5\cdot + HgC_2H_5$$
$$HgC_2H_5 \rightarrow C_2H_5\cdot + Hg$$
$$2\ C_2H_5\cdot \rightarrow C_4H_{10} \qquad \text{(III)}$$
$$2\ C_2H_5\cdot \rightarrow C_2H_4 + C_2H_6$$

etc.

Many investigators have studied the behavior of organomercurials upon irradiation.

Linnet and Thomson (5) studied the photolysis of mercury dimethyl under the influence of ultraviolet light (2537 A°) and found that metallic mercury and ethane with a small amount of other hydrocarbons were the products.

The quantum efficiency of the decomposition at room temperature was found to be unity. This fact was explained by the hypothesis that the primary act is (IV).without the production of reaction

$$Hg(CH_3)_2 + h\nu \rightarrow Hg + C_2H_6 \qquad \text{(IV)}$$

chains.

Later (6) they investigated the effect of temperature and of the presence of nitric oxide on the reaction. They assumed that if chains are appreciably propagated in the photolysis this effect should become more marked at higher temperatures. On the other hand the presence of

nitric oxide would retard the decomposition by breaking the reaction chains by interaction with free methyl radicals.

They concluded that the higher overall quantum efficiency obtained at higher temperatures [$\gamma = 2$ at 462°C] and the results in the presence of nitric oxide (formation of a solid deposit and decrease in the total pressure) favored a free radical mechanism. They suggested the following scheme (V).

$$Hg(CH_3)_2 + h\nu \rightarrow HgCH_3 + \cdot CH_3 \quad (1)$$

$$HgCH_3 \rightarrow Hg + \cdot CH_3 \quad (2)$$

$$Hg(CH_3)_2 + HgCH_3 \rightarrow Hg + C_2H_6 + HgCH_3 \quad (3)$$

$$\cdot CH_3 + Hg(CH_3)_2 \rightarrow HgCH_3 + C_2H_6 \quad (4) \qquad (V)$$

$$\cdot CH_3 + Hg(CH_3)_2 \rightarrow Hg + \cdot CH_3 + C_2H_6 \quad (5)$$

$$2 \cdot CH_3 \rightarrow CH_3CH_3 \quad (6)$$

$$\cdot CH_3 + HgCH_3 \rightarrow C_2H_6 + Hg \quad (7)$$

$$2\ HgCH_3 \rightarrow Hg + C_2H_6 \quad (8)$$

In this scheme (V-3,4,5) are the chain propagating stages. In order that the reaction shall have a quantum yield of unity in terms of disappearance of mercury dimethyl it was assumed that stages (V-3,4,5) involve a high energy of activation. At higher temperatures the acquisition of the energy of activation required for processes (V-3,4,5) will lead to chain propagation and γ will rise above unity. The quantum efficiency in the decomposition of mercury dimethyl in the presence of nitric oxide at room temperature was found close to unity. This result was taken by Linnet and coworkers as an indication that the quantum yield of the primary process (V-1) is really unity and it is understandable if the nitric oxide reacts only with the free radicals formed by the primary process.

Gomer and Noyes (7) studied recently the rates of photolysis of mercury dimethyl as functions of intensity, pressure and temperature. They took the initial process to be the formation of free radicals (VI-1). They concluded that at temperatures below 250° methane is formed by the reaction (VI-2) followed by a recombination step (VI-3).

$$(CH_3)_2Hg \xrightarrow{h\nu} \cdot CH_3 + CH_3Hg \quad (1)$$

$$\cdot CH_3 + CH_3HgCH_3 \rightarrow CH_4 + \cdot CH_2HgCH_3 \quad (2) \qquad (VI)$$

$$\cdot CH_3 + \cdot CH_2HgCH_3 \rightarrow CH_3CH_2HgCH_3 \quad (3)$$

Ethane is formed by collision of two methyl radicals (VII-1) or by the reaction of the methyl radical with dimethylmercury, a reaction which they took to proceed through an unstable intermediate complex (VII-2,3),

$$2 \cdot CH_3 \rightarrow C_2H_6 \quad (1)$$

$$\cdot CH_3 + Hg(CH_3)_2 \rightleftharpoons A \quad (2) \qquad \text{(VII)}$$

$$\cdot CH_3 + A \rightarrow C_2H_6 + Hg + 2 \cdot CH_3 \quad (3)$$

Kazuvayev and his coworkers (8) studied extensively the photolysis of organomercurials in different solvents like carbon tetrachloride chloroform, other chlorinated hydrocarbons, alcohols, benzene, etc.

From the products obtained they postulated that in all cases the initial process is the dissociation of the organomercurials to free radicals (VIII).

$$ArHgAr' \rightarrow ArHg + Ar'. \qquad \text{(VIII)}$$

These free radicals then react with the solvent as in the examples given below.

a. In carbon tetrachloride

$$ArHg + CCl_4 \rightarrow ArHgCl + \cdot CCl_3$$

$$Ar\cdot + CCl_4 \rightarrow ArCl + \cdot CCl_3$$

$$2 \cdot CCl_3 \rightarrow Cl_3C\text{-}CCl_3$$

b. in chloroform

$$ArHg + CHCl_3 \rightarrow ArHgCl + \cdot CHCl_2$$

$$Ar\cdot + CHCl_3 \rightarrow ArH + \cdot CCl_3$$

$$2 \cdot CCl_3 \rightarrow C_2Cl_6$$

c. in alcohols

$$ArHg\cdot + RCH_2OH \rightarrow ArH + R\dot{C}HOH + Hg$$

$$Ar\cdot + RCH_2OH \rightarrow R\dot{C}HOH + ArH$$

$$R\dot{C}HOH \rightarrow RCH{=}O + H\cdot$$

$$H\cdot + ArHg \rightarrow ArH + Hg$$

$$H\cdot + Ar\cdot \rightarrow ArH$$

ACID DECOMPOSITION OF ORGANOMERCURIALS

The acid cleavage of aromatic mercurials was recognized by Kharasch (9) as a valuable tool in the general problem of aromatic substitution. Kharasch has assumed that the step which determines the composition of the reaction products is an ionization of the type (IX).

$$Ar\text{-}Hg\text{-}Ar' \rightarrow Ar\text{-}Hg^{\oplus} + Ar^{\ominus} \qquad IX$$

The ionization is then followed by combination with the ions of the acid employed (X).

$$ArHg^{\oplus} + Ar'^{\ominus} + H^{\oplus} + X^{\ominus} \rightarrow ArHgX + Ar'H \qquad (X)$$

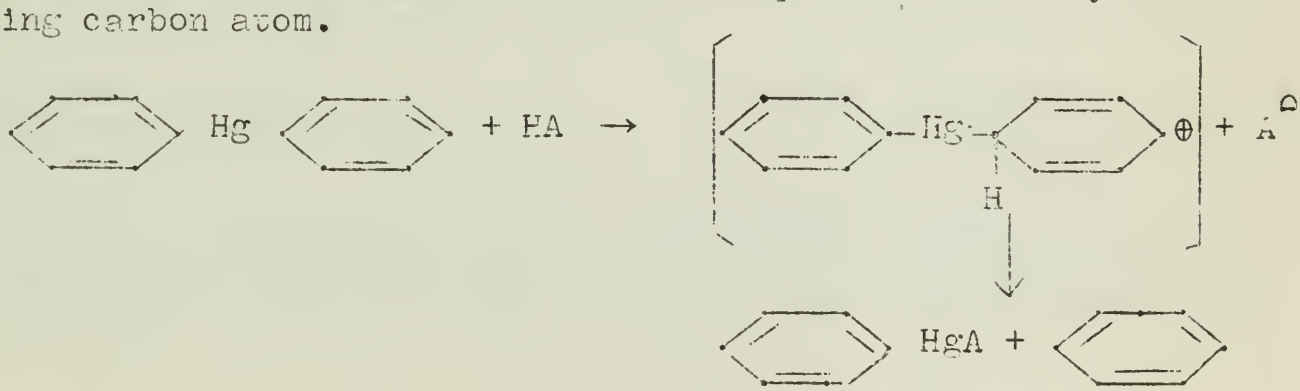
The group Ar' which first dissociates from the mercury and then combines with the hydrogen ion in solution to form the hydrocarbon Ar'H was defined by Kharasch as the more electronegative of the two groups, that is it has the greater attraction for electrons.

This criterion was used by Kharasch and his coworkers in a study of the acid cleavage of asymmetric organomercurials in an attempt to determine the relative electronegativities of different organic groups. As a result of their investigation Kharasch et al. arranged the studied organic radicals in order of decreasing electronegativity as follows: p-methoxyphenyl > o-methoxyphenyl > α-naphthyl > o-tolyl > p-tolyl > m-tolyl > phenyl > p-chlorophenyl > o-chlorophenyl > m-chlorophenyl > methyl > ethyl > propyl > butyl > heptyl > benzyl > ethylphenyl.

Corwin and Naylor (10,11) observed that the above electronegativity series deduced by Kharasch is in almost exactly the same sequence as those deduced by Hammett and other investigators (9-11) but in inverted order. Studying the acid cleavage of diphenylmercury they showed that Kharasch's proposed ionization mechanism failed to account for the experimental results. The cleavage rate of diphenylmercury was found to be strongly dependent on the strength of the acid used and it was not strongly affected by increasing the dielectric constant of the solvent.

They concluded that a mechanism of acid attack leading to a protonated intermediate was in agreement with experiment (XI).

This mechanism explains the rate dependence on acid strength as well as the products obtained by Kharasch in the cleavage of unsymmetrical mercurials in terms of an electrophilic attack by acid on the ring carbon atom.



XI

A free radical mechanism was ruled out by the absence of products such as diphenyl, or phenol and by the independence of the observed rate on peroxide concentration (11).

However, A. A. Bolshakova (12) studying the decomposition of methyl-α-naphthyl and methylphenylmercury by mono- and dibasic organic acids, on the basis of the experimentally obtained products, postulated the following free radical mechanism for the reaction (XII).

$$CH_3HgAr \rightarrow CH_3Hg + Ar\cdot$$
$$Ar\cdot + RCOOH \rightarrow ArH + RCOO\cdot \qquad \text{(XII)}$$
$$CH_3Hg + RCOO\cdot \rightarrow RCOOHg\cdot CH_3$$

They concluded that the less reactive methyl radical remains bound to the mercury atom and in such form it is transferred into the composition of the acid derivative.

Such a mechanism is entirely unsubstantiated. Decomposition of metal organic compounds of mercury into radicals proceeds at temperature much above 75°C. Furthermore the Ar-radicals should have removed the hydrogen atoms from the α-carbon atom of the chain (13,14) and to a lesser extent from the carboxyl. Finally were the RCOO· radical to appear, it would have to have a sufficient half-life period without decomposing, in order to encounter the $CH_3Hg\cdot$ radical. In the meantime it is expected that the RCOO· radicals would decompose at 75° to R· and CO_2 (15). It is not understood why the methyl radical is considered less reactive than the naphthyl or phenyl radical. On the contrary it is known that the most reactive is the non-stabilized methyl radical (13).

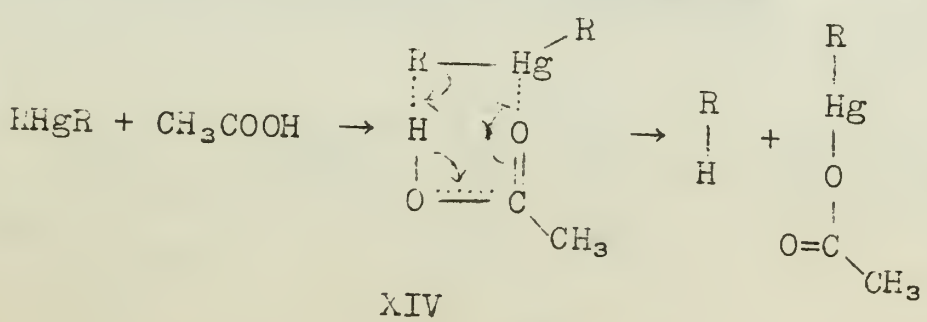
STUDY OF ELECTROPHILIC SUBSTITUTION ON SATURATED CARBON ATOM USING ORGANOMERCURIALS

Winstein and Traylor (16) investigated the acetolysis of dialkylmercury compounds as an example of electrophilic substitution on carbon. They observed good first order kinetics for the reaction (XIII) where R = s-butyl, n-butyl and neophyl. Acetolysis stops

$$R_2Hg + AcOH \rightarrow RH + RHgOAc \qquad \text{(XIII)}$$

cleanly with cleavage of the first alkyl group, cleavage of the second group being extremely slow.

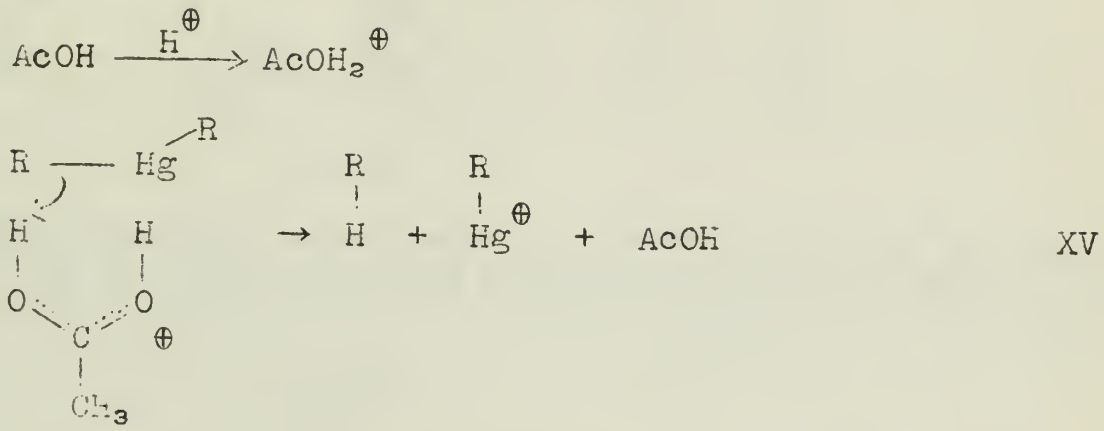
An S_Ei mechanism (XIV) was postulated on the basis of possible combinations of electrophilic and nucleophilic species for first order acetolysis of a carbon-mercury bond, and from the absence of any appreciable effect of added acetate ion on rate of acetolysis.



XIV

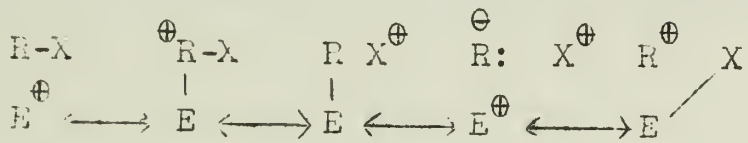
Acid catalyzed solvolysis of the above mentioned dialkylmercury compounds involving perchloric acid in glacial acetic acid was found to follow second order kinetics.

An S_E2 mechanism was suggested (XV).



XV

The rate of acetolysis of mercury diphenyl exceeds very substantially that of dialkylmercury. The sequence $(C_6H_5)_2Hg$ $(S\text{-}Bu)_2Hg$ $(n\text{-}Bu)_2Hg$ $(neophyl)_2Hg$ was explained by Winstein and Traylor in relation to the transition state (XVI' for electrophilic substitution on RX by E. The greater reactivity of the aryl group may be explained by reference to contributions of structures such as XVIb. The effect

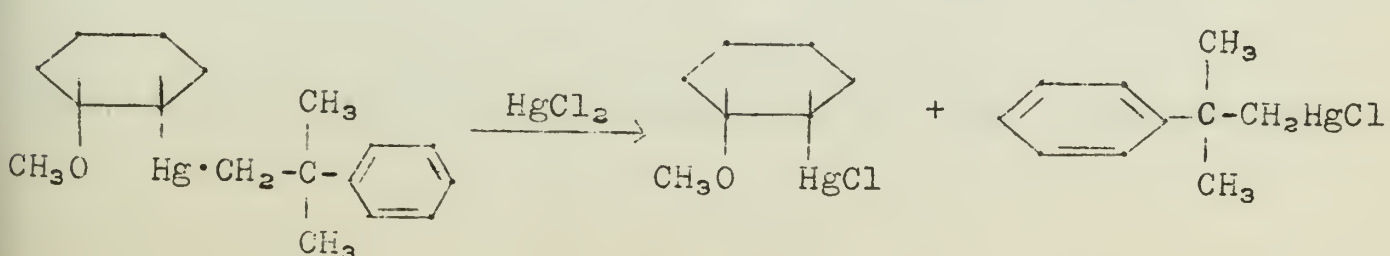


XVIa b c d e

on variation in R on rate will depend on the importance of bond making and breaking (XVIc,d). Another consideration is possible bonding between X and E with consequent cationic character on R (XVIe). The effects of substituents on X are especially serious. For example, rates of electrophilic substitution on R are enormously greater for X = HgR than for X = HgCl.

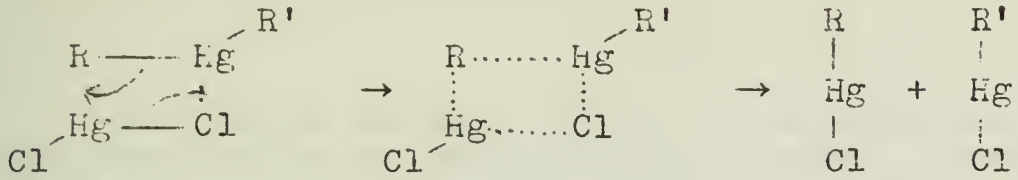
The same rate sequence S-Bu > n-Bu was also observed in the rates of butane evolution by the action of concentrated hydrochloric acid in the dibutylmercury compounds (17).

Winstein and Traylor (18) observed that electrophilic displacement by mercuric chloride on <u>cis</u> 2-methoxycyclohexylneophyl mercury (XVII) proceeds with retention of configuration.



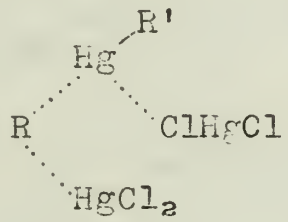
XVII

From that observation, in the absence of a kinetic study which would disclose the composition of the transition state, a cyclic or 4-center mechanism was suggested (XVIII).



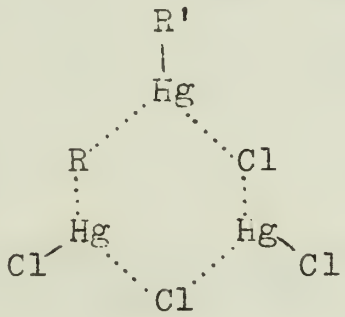
XVIII

Another possible mechanism is a variation of the S_E2 type, involving one mercuric chloride molecule in an electrophilic role and another in a nucleophilic one as in the transition state (XIX).



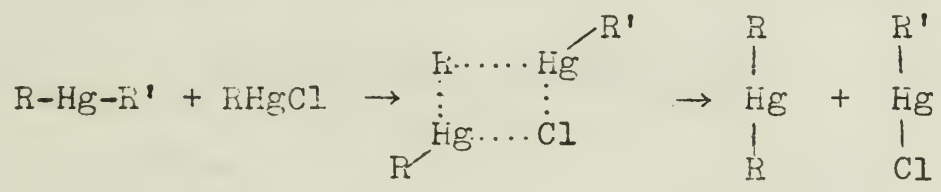
XIX

Other possible bonding interactions are not indicated in the transition states XVIII and XIX. For example the two attacking mercuric chloride molecules in XIX may be coordinated through a chlorine atom as in XX.



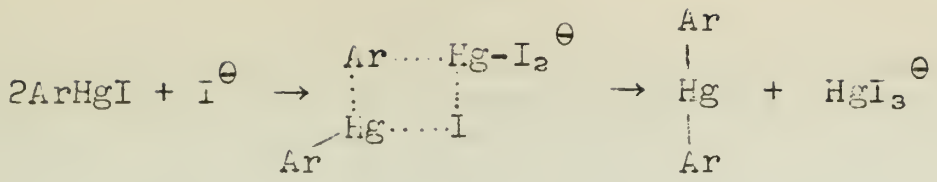
XX

Another reaction with probably an analogous mechanism is the disproportionation of dialkylmercuric compounds by alkylmercuric chloride, RHgCl, a poorer electrophile than mercuric chloride (XXI) (19). The formation of diarylmercury by the action of iodide ion on



XXI

arylmercuric iodide may be presented by the same mechanism (XXII)(20).



XXII

In relation to the problem of stereochemistry in the electrophilic substitution on saturated carbon atom, Winstein and Traylor (21) studied electrophilic substitution reactions at the bridgehead of 4-camphylmercurials.

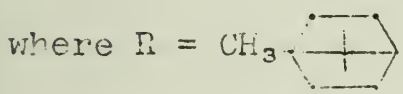
Bridgehead displacements are of interest because of the information that they provide about the possible stereochemistry of the various displacement reactions. Because backside approach of the attacking reagent and inversion of configuration are prohibited at a bridgehead, reactions which can proceed only by inversion mechanism cannot occur at bridgehead (22).

The investigated electrophilic substitution reactions included the reaction between di-4-camphylmercury (XXIII) and mercuric chloride, neutral first order and acidic second order acetolysis of di-4-camphyl mercury (XXIV) and the second order reaction between 4-camphyl-iodide (XXV) and triiodide ion in slightly aqueous dioxane.

$$R\text{-}Hg\text{-}R + HgCl_2 \rightarrow 2RHgCl \qquad (XXIII)$$

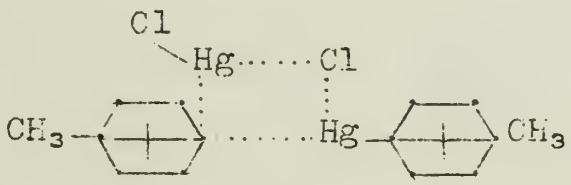
$$R\text{-}Hg\text{-}R + AcOH \rightarrow RH + RHgOCOCH_3 \qquad (XXIV)$$

$$RHgI + I_3^{\ominus} \rightarrow RI + HgI_3^{\ominus} \qquad (XXV)$$

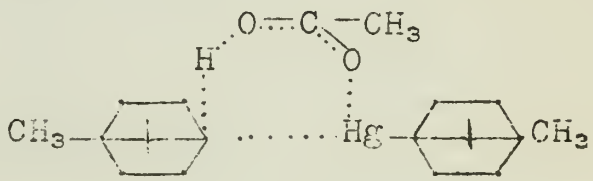
where R = 

All of the electrophilic substitutions of the 4-camphylmercury derivatives necessarily proceed with retention of configuration.

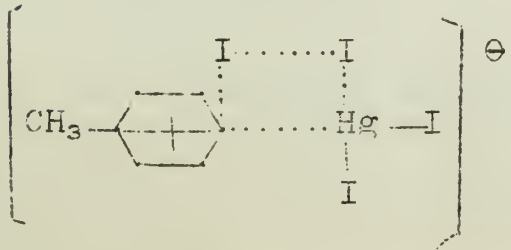
An S_Ei mechanism was suggested by Winstein and Traylor (21). The transition states might be pictured respectively as follows:



XXIIIa

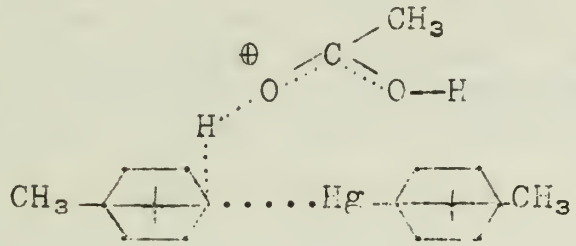


XXIVa



XXVa

Winstein and Traylor (21) also found that di-4-camphylmercury solvolyzes in acetic acid at a greatly enhanced rate if perchloric acid is added. Rough second order kinetics were observed first order in the mercurial and first order in the acid. It is believed that this can be accounted for only by an S_E2 displacement at the bridgehead with a hydrogen ion displacing a 4-camphylmercuric ion. The transition state of the reaction is pictured below (XXVI).



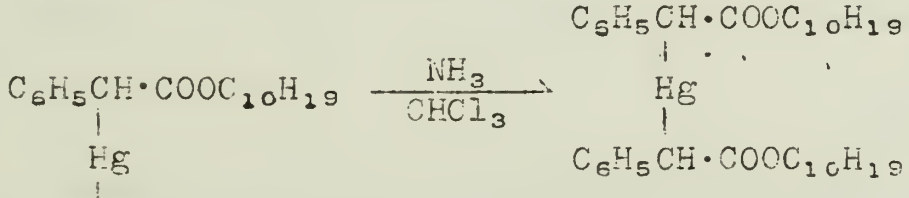
(XXVI)

Further insight into the nature of these substitution reactions may be gained from the observed relative reactivities of the bridgehead mercurials compared to non-bridgehead derivatives.

The 4-camphylmercury derivatives occupy an intermediate position between neophyl and n-butyl with respect to reactivity toward triiodide ion, acetic acid and perchloric acid.

Thus there is no indication that the bridgehead derivatives are forced to react by a mechanism leading to retention because a much more preferable one is excluded by the bridgehead restriction. From the fact that complete retention was also observed in the substitution reaction of methoxycyclohexylneophylmercury with mercuric chloride, from the relative rates of substitution and especially from the fact that the second order acidic solvolysis of the dialkyl mercurials gives products with retention of configuration, Winstein and Traylor suggested that retention of configuration in electrophilic substitution at saturated carbon atom may be general.

Nesmeyanov and coworkers (23) reported that each pure diastereomeric l-menthoxy α-phenyl-α-bromomercuriacetate (XXVII) reacts stereospecifically with ammonia in chloroform to yield pure LL-LL or DL-DL dialkylmercury (XXVIII) with retention of configuration.



XXVII XXVIII

The retention of configuration in the formation of XXVIII from XXVII is in line with the work of Winstein and Traylor. However, the reaction of XXVIII with mercuric bromide in boiling acetone was reported (23) to be non-stereospecific, the same approximately equimolar mixture of diastereomers of XXVII being derived from each pure XXVIII.

Winstein (21) expressed the opinion that the presence of both a phenyl and a carboalkoxy group on the asymmetric carbon atom in XXVIII would seriously affect matters.

Further investigations of this and other structures are desirable.

4-camphylmercuric iodide reacts with iodine in dioxane to give 4-iodocamphane in good yields (XXIX). Heller (24) postulated the following free radical mechanism. The free radical character of this reaction is indicated by its inhibition by oxygen, by the irregularity of reaction rates, and by sensitivity to light and peroxides.

$$I\cdot + RHgI \rightarrow R\cdot + HgI_2$$

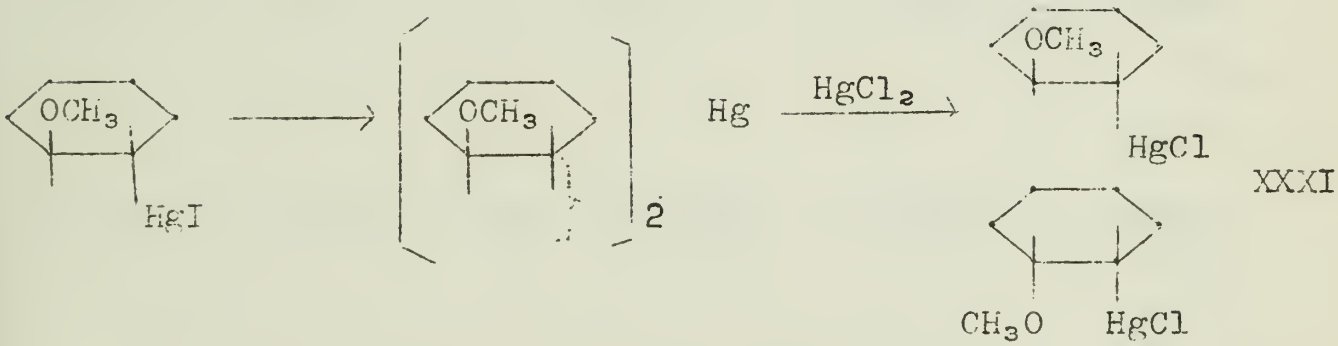
$$R\cdot + I_2 \rightarrow RI + I\cdot \qquad \text{XXIX}$$

where R· = CH_3  .

A free radical intermediate is considered probable in the reduction of 4-camphylmercuric chloride to di-4-camphylmercury by treatment with sodium stannite (XXX) because the analogous reduction of trans 2-methoxycyclohexylmercuric iodide with sodium stannite and cleavage of the resulting dialkylmercury with mercuric chloride (a stereospecific S$_E$i reaction gives a mixture of cis and trans 2-methoxycyclohexyl chlorides (XXXI).

$$RHgCl \rightarrow R\cdot HgR \qquad \text{XXX}$$

where R = CH_3  .



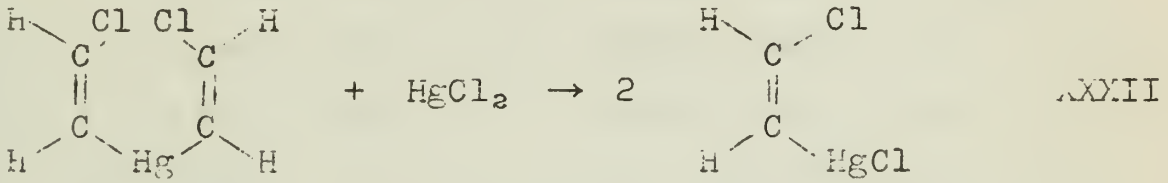
XXXI

A reaction probably involving a free carbanion as intermediate is the reduction of 4-camphylmercuric chloride to camphane with lithium-aluminum hydride carried by Winstein and Traylor (21).

The ease with which the above mentioned bridgehead reactions involving free radicals and anion proceed is explained with the hypothesis of permissible pyramidal configuration of radicals and anions (22).

STUDY OF ELECTROPHILIC SUBSTITUTION AT OLEFINIC CARBON ATOM USING ORGANOMERCURIALS

Nesmeyanov, Reutov et al. carried a number of investigations dealing with the stereochemistry of electrophilic and homolytic exchange at the olefinic carbon atom, using organomercurials (25). For example, bis-2-chlorovinylmercury reacts with mercuric chloride with retention of configuration (XXXII) (26).



XXXII

Retention of configuration at a trigonal carbon atom is common in other conversions of vinyl compounds (27).

where X=Br E=Li; X=I i E=CO_2; X=COOH

E=H; X=Cl E=H; X=C_6H_5CO E=H

Using odd and even cycles Nesmeyanov and his coworkers concluded that in general electrophilic or homolytic substitution at olefinic carbon atom proceeds with retention of configuration (25).

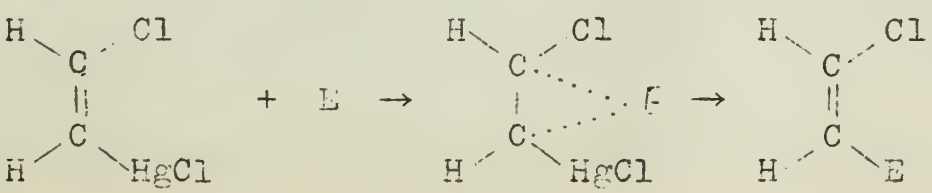
For cis-bromostilbene we have for example (28).

3 cycles-cis-StBr $\xrightarrow{C_4H_9Li}$ St·I i $\xrightarrow{HgCl_2}$ St_2Hg $\xrightarrow{Br_2}$ StBr (cis)

4 cycles-cis-StBr ⟶ St·Li ⟶ St_2Hg $\xrightarrow[HgBr_2]{}$ StHgBr $\xrightarrow{Br_2}$ StBr (cis)

5 cycles-cis-StBr → StLi → St_2Hg → StHgCl → $StSnCl_3$ $\xrightarrow{Br_2}$ StBr (cis)

Regarding the mechanism of threse reactions Nesmeyanov pointed out that the only plausible conclusion would be to assume the formation of a complex in the transition state retaining the configuration (XXXIII) (25).



XXXIII

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THE BENZYNE INTERMEDIATE

Reported by W. Kenneth Musker October 17, 1957

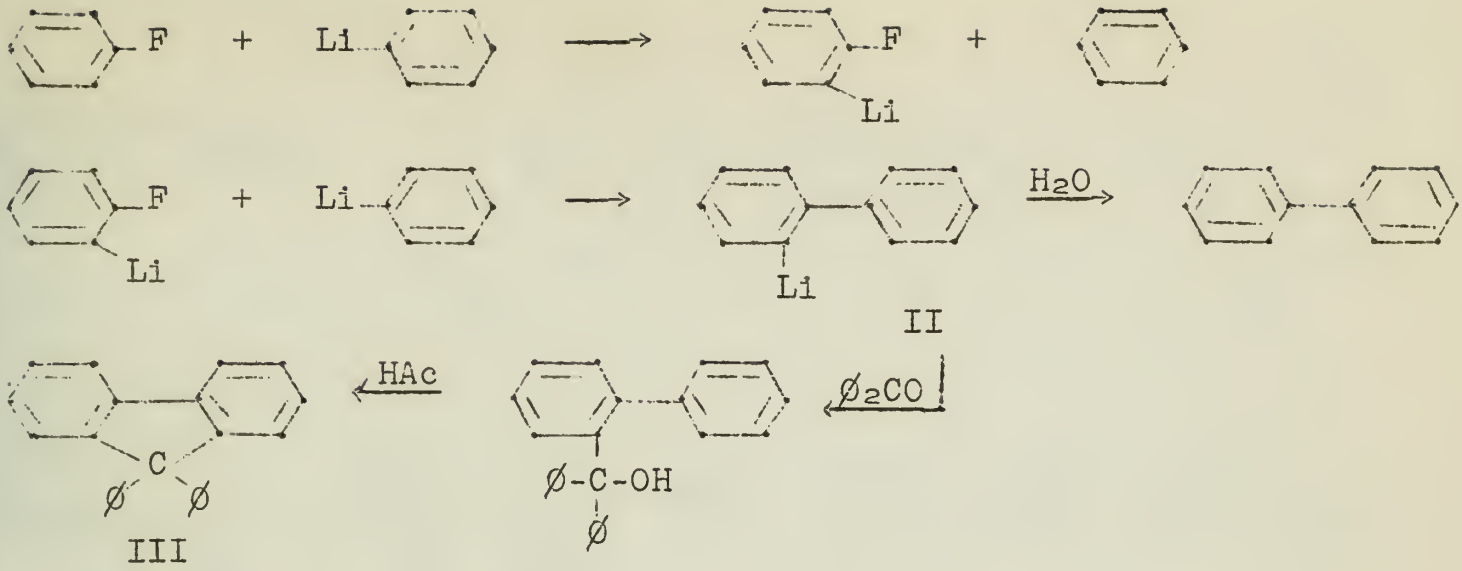
The term "cine-substitution" (1) has been used to classify a number of nucleophilic aromatic substitution reactions in which the position of the entering group is adjacent to the leaving group. Some of these reactions can be reconciled by the use of a cyclic mechanism, as in the displacement of a nitro group by cyanide ion in the von Richter reaction (2,3); an addition mechanism followed by rearrangement, as in the displacement of a bromide ion from bromothianaphthene by piperidine (4); and, most recently, a mechanism involving the use of a benzyne intermediate, as in the displacement of halogen from aromatic halides by amide or hydroxyl ions. The purpose of this seminar will be to present the available evidence for the existence of the "benzyne intermediate" and to describe reactions which can be explained on the basis of this intermediate. The subject of cine-substitution was discussed recently in an M.I.T. seminar by Liss (17) and the isotopic evidence for benzyne was presented at Illinois in 1955 by Pedrotti (18).

In 1892, Kym reported that when 1-halonaphthalenes were treated with aniline or toluidine at 300°-350°C., a rearrangement occurred giving the corresponding 2-aminonaphthalenes (5). Due to the high temperatures involved and low yields of products, these amination reactions were not investigated extensively until 1936 when Bergstrom et. al. (6) found that aryl halides could be aminated in good yields by the use of potassium amide in liquid ammonia or lithium diethylamide in ether. However, little speculation was advanced for the mechanisms of these reactions.

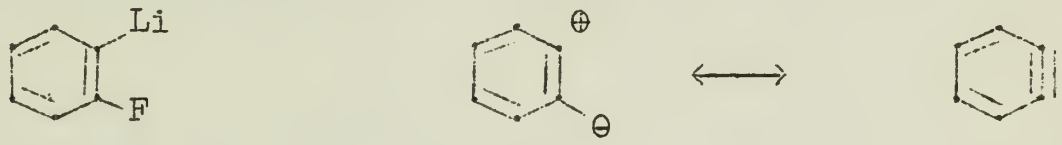
In 1927, Bachman and Clark (29) assumed a free phenylene intermediate to account for the formation of triphenylene in a coupling reaction of chlorobenzene with sodium. This involved the interaction of two phenyl ~~anions~~ RADICALS to produce benzene and free phenylene. The free phenylene condensed with itself to form triphenylene.

$$2C_6H_5^{\bullet} \longrightarrow C_6H_6 + C_6H_4$$

In 1942, Wittig noted that when halobenzenes were condensed with phenyllithium, fluorobenzene gave a 70% yield of biphenyl (I), while all the other halides gave less than a 10% yield. Although diphenyl was the final product of the reaction, Wittig found the precursor, o-diphenyllithium (II), by treating the reaction mixture with benzophenone and subsequent cyclization to give 9,9-diphenylfluorene (III). These reactions can be formulated in the following way (7):

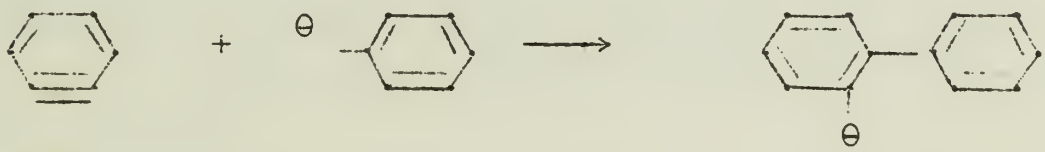


Wittig reasoned that the increase in the yield of biphenyl with the aryl fluoride was due to the inductive effect of the electronegative fluorine atom which facilitated the exchange of a proton with a lithium cation at the ortho position (greatest inductive effect). o-Fluorophenyllithium then condensed with phenyllithium to produce II. Wittig further proposed that o-fluorophenyllithium (IVa), having a strong electronegative atom adjacent to lithium, would lose lithium fluoride to give a dipolar structure, which is but a resonance structure of a compound having a triple bond (IVc).



IVa IVb IVc

IVa was then presumed to react with phenyllithium in the following way to produce II.

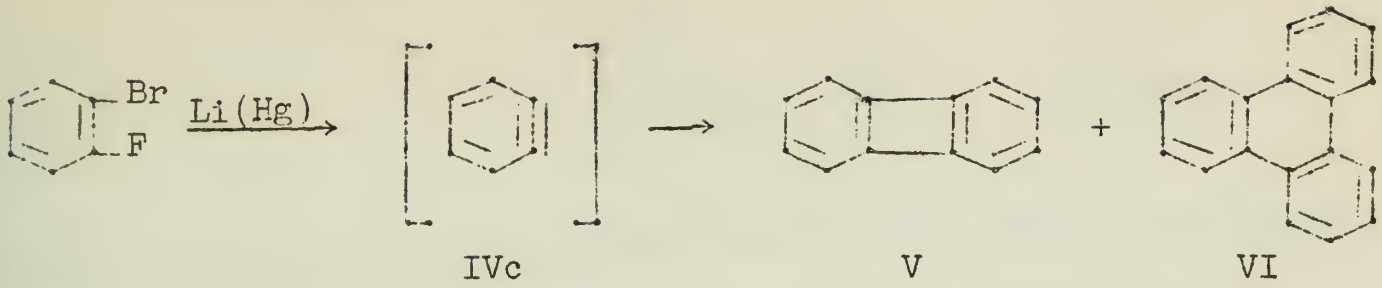


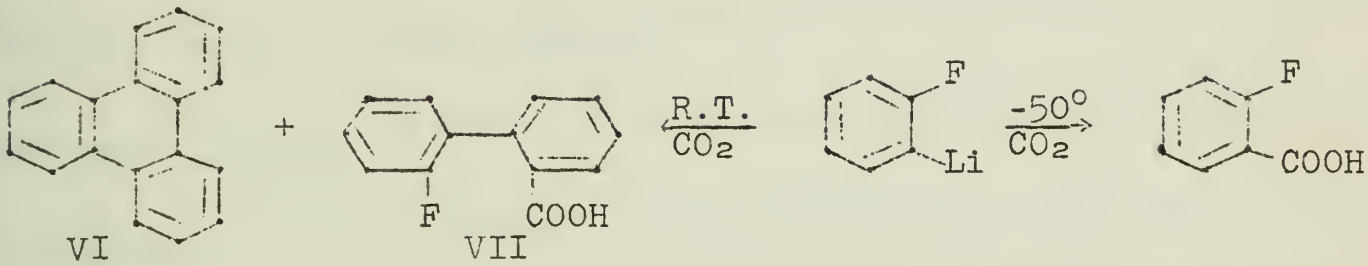
IVc II

The structure which contains the triple bond (IVc) was denoted as dehydrobenzene by Wittig (7), benzyne by Roberts (10,11), arin by Huisgen (34), and free phenylene by Bachman (29).

Wittig (13,14) attempted to synthesize o-fluorophenyllithium by shaking o-fluorobromobenzene with lithium amalgam in ether. However, the only products isolated were diphenylene (V) and triphenylene (VI). These he assumed could result from the condensation of two and three molecules of benzyne respectively. Recently, Gilman and Gorsich (8,9) have synthesized o-bromo, o-chloro-, and o-fluorophenyllithium by operating at temperatures below -50°C. By carbonating the reaction mixture at -50°, an 83% yield of o-fluorobenzoic acid was obtained. However, when the reaction mixture was warmed to room temperature only 2-fluoro-2'-carboxybiphenyl (VII) and triphenylene

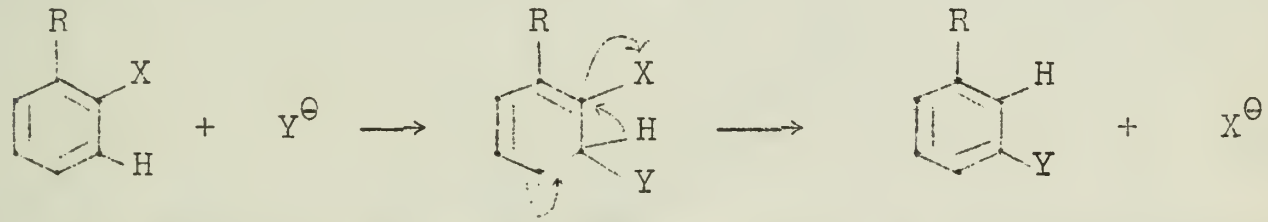
(VI) were obtained.





The formation of a triple bond by the reaction of a lithium reagent on an alkenyl halide is not new, for it is known that acetylenic compounds can be formed by this reaction.

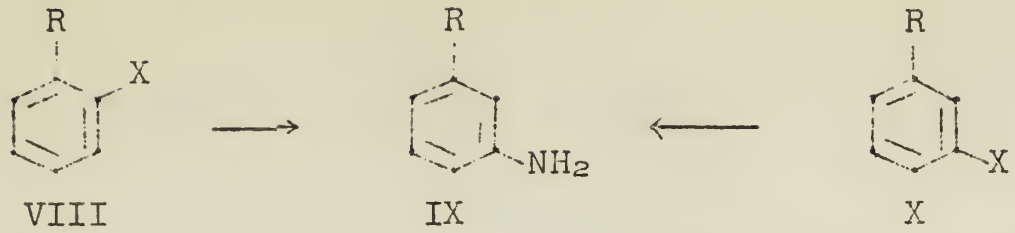
Wittig's early concept of a benzyne intermediate received little attention since it was felt that the rearrangements which occurred must rather proceed by the attack of an anion on the carbon atom ortho to the halogen atom with simultaneous or subsequent hydride transfer and elimination of the halogen (1,15,16).



Evidence for the benzyne intermediate, or at least a symmetrical intermediate, was presented by Roberts, et. al. in 1953 (10). After considering the following experimental observations (17,18,11) in the reactions of aromatic halogen compounds with metallic amides, a reaction was devised which utilized a carbon-14 tracer to follow the course of the carbon atom bonded to the halogen atom through the reaction sequence.

1a. Ortho-substituted halobenzenes (VIII) with the substituent R = $-OCH_3$, $-OC_6H_5$, $-OH$, $-N(CH_3)_2$, $-CF_3$, $-SCH_3$, and $-SO_2CH_3$, and X = I, Br, and Cl give meta substituted anilines IX free from ortho and para isomers. Fluorobenzenes are not aminated at an appreciable rate under the reaction conditions.

b. Aminations of meta substituted halobenzenes (X) R = $-OCH_3$, $-CF_3$ produce only the meta-anilines (IX). (These rearrangements show a complete disregard for the usual influences which govern aromatic substitutions.)



VIII IX X

2. Treatment of 1-fluoronaphthalene with lithium diethylamide gives 2-diethylaminonaphthalene.

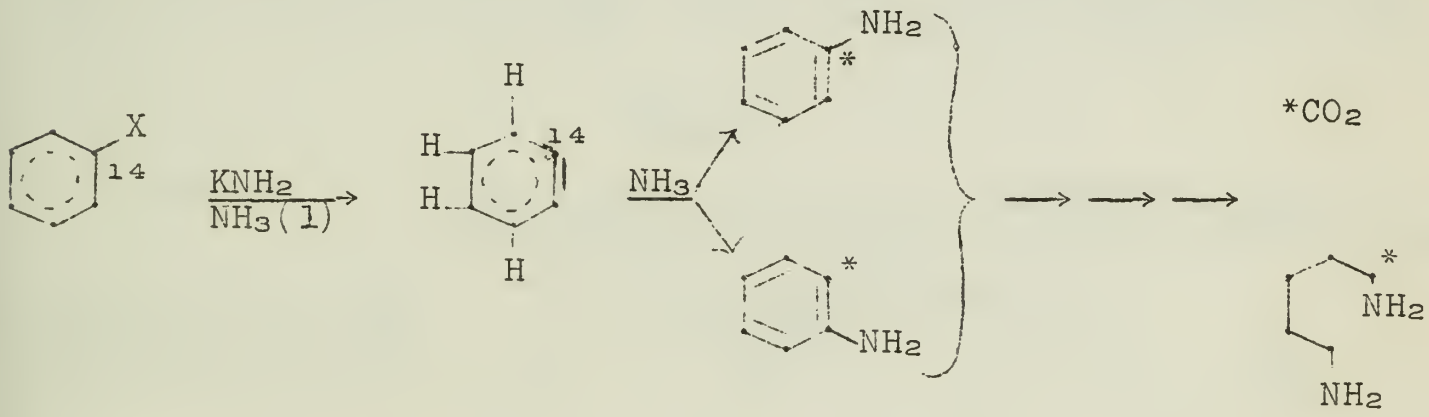
3. The reactions of the halobenzenes with alkali metal amides are very rapid in liquid ammonia.

4. The entering group is never more than one carbon away from the leaving group.

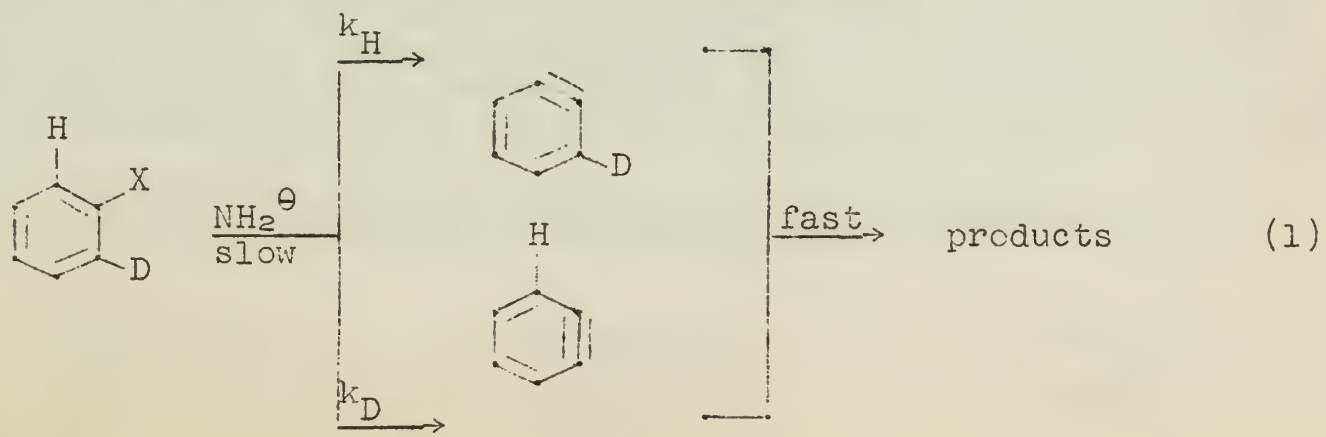
5. The starting halides are not isomerized under the reaction conditions.

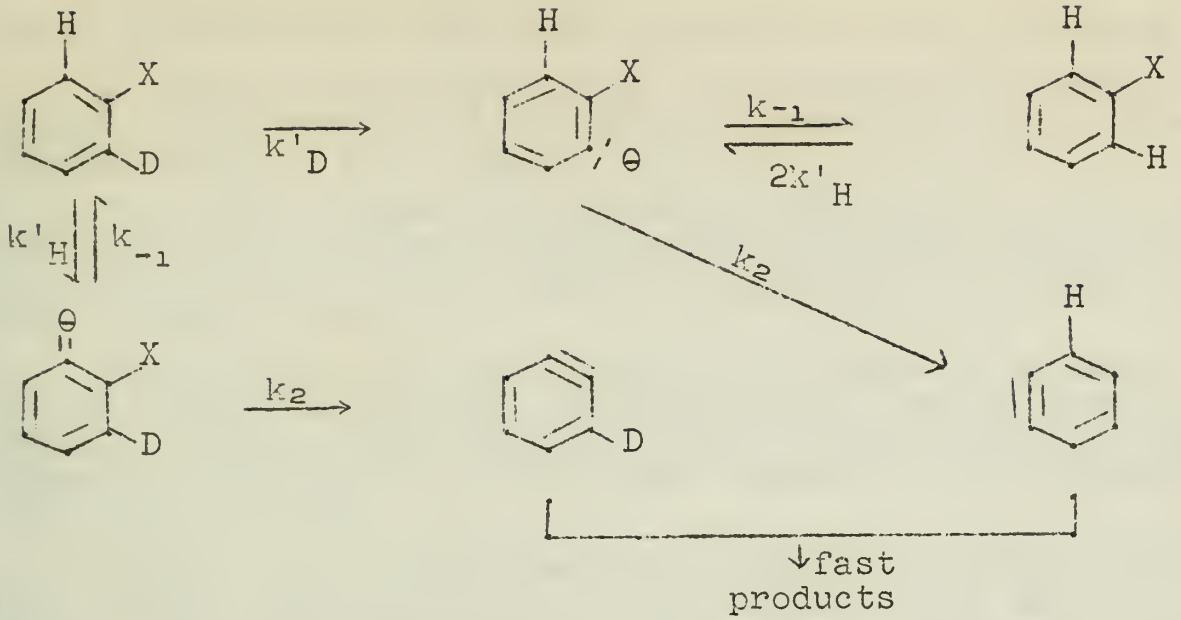
6. No reaction occurs unless a hydrogen atom is adjacent to the position occupied by the leaving halogen. (Bromomesitylene and 2-bromo-3 methyl anisole do not react.)

Both iodobenzene-1-^{14}C and chlorobenzene-1-^{14}C were treated with potassium amide in liquid ammonia and the resulting anilines were degraded to CO_2 and 1,5-diamino pentane. The 54% rearrangement which was found in both cases is within the estimated isotope effect and renders unlikely the possibility of the usual displacement reactions.



The 1,2 elimination of HX may proceed by a concerted process (1) or a stepwise process (2). These two mechanisms can be distinguished by the use of halobenzenes-2-^{2}H (^{2}H = deuterium).





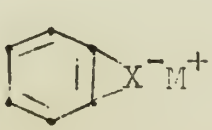
If the reaction proceeds by a concerted process (1), an isotope effec· (kH/kD) of 6-7 is expected. (An isotope effect of 6.7 is observed for the concerted elimination of HBr from isopropyl bromide (13).) If the stepwise mechanism is obeyed, the isotope effect should be much lower due to the fact that the anions formed in the initial step may abstract a proton from the solvent and revert back to starting materials. The magnitude of the apparent isotope effect is thus affected by the ratio (k_{-1}/k_2). The composition of the recovere· starting material was determined by an infrared technique and the ratio (kH/kD) was calculated by assuming the concerted mechanism (1). When fluoro-, chloro-, and bromobenzene were treated with potassium amide in liquid ammonia and with lithium diethylamide in ether, the isotope effectswere calculated and are tabulated in Table 1.

TABLE 1

Compound	KNH_2 in NH_3		$LiN(Et)_2$ in Et_2O	
	mechanism	kH/kD(apparent)	mechanism	kH/kD(apparent
fluorobenzene-2-^{2}H	no appreciable amination			
chlorobenzene-2-^{2}H	2	2.88	1	5.7
bromobenzene-2-^{2}H	1	5.7	1	5.6

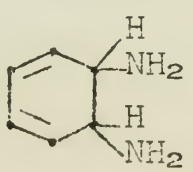
Since the ortho hydrogen is removed as a positive ion, the rate of this process would be expected to follow the order F > Cl > Br > I. However, the rate sequence expected for the loss of halide would be I > Br > Cl > F. The change from mechanism (2) to (1) occurs when the loss of halide becomes much easier than the readdition of a proton so that the steps become synchronized. The order of reactivity of the halobenzenes toward amide ion was found to be Br > I > Cl >> F.

In addition to the benzyne intermediate proposed by Roberts, other possible symmetrical intermediates can be assumed (10,11).



XIa

XIb



XIc

These intermediates have been discounted in the following ways.

It seems very unlikely that fluorocompounds would use their higher energy orbitals to accomodate ten electrons in forming a bridged compound as in XIa.

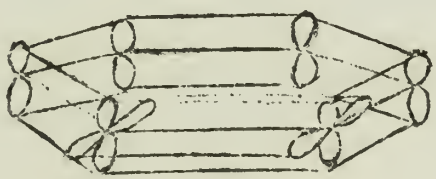
The cation complex XIb would be analogous to silver-alkene complexes, but it seems unlikely that an alkali metal cation would coordinate with a double bond in the presence of a high concentration of amide ions.

Intermediate XIc would have to be formed by an addition-substitution mechanism and would decompose with loss of ammonia to the aniline. The initial step of adding ammonia across an aromatic double bond would be an endothermic reaction by 25 kcals/mole and therefore unlikely.

Morton (20) has proposed a 1,3 addition process involving an ior pair concept and pictured the intermediate as an additive product (XII). This ion pair concept has not been verified by experimental evidence and does not seem to differ greatly from the addition-rearrangement-elimination mechanism proposed earlier (16).

The fact that both iodobenzene-1-^{14}C and chlorobenzene-1-^{14}C gave a 54% rearrangement would be difficult to explain on the basis of this mechanism. Roberts (21) also refutes this mechanism "on quantum mechanical grounds".

Roberts benzyne molecule can be pictured in the following manner The strain involved in such a molecule is comparable to that in cyclo propene, and it is interesting to note that a bent excited state of acetylene has been found by spectral studies (11).

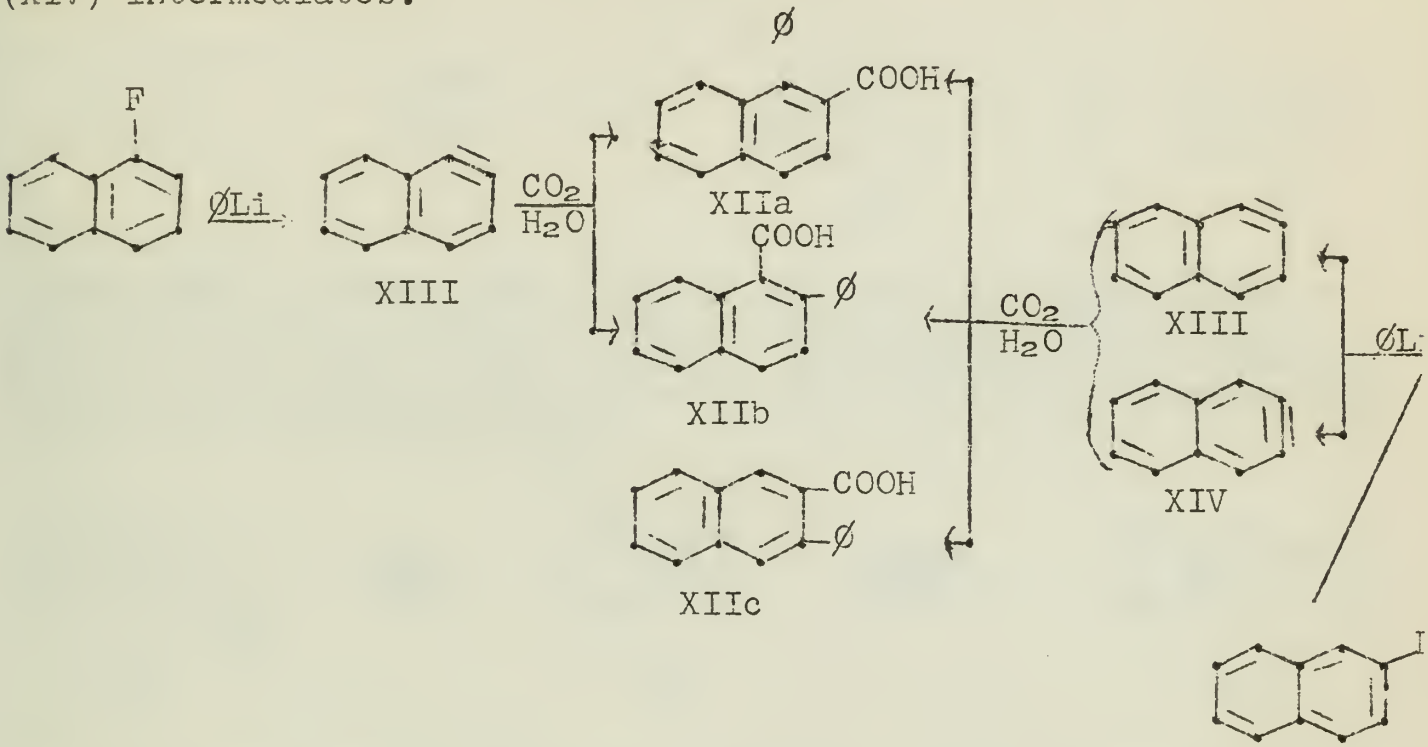


The orientation of the entering amine group can be predicted in cases of negligible steric effect by considering the inductive effect of the substituents (19).

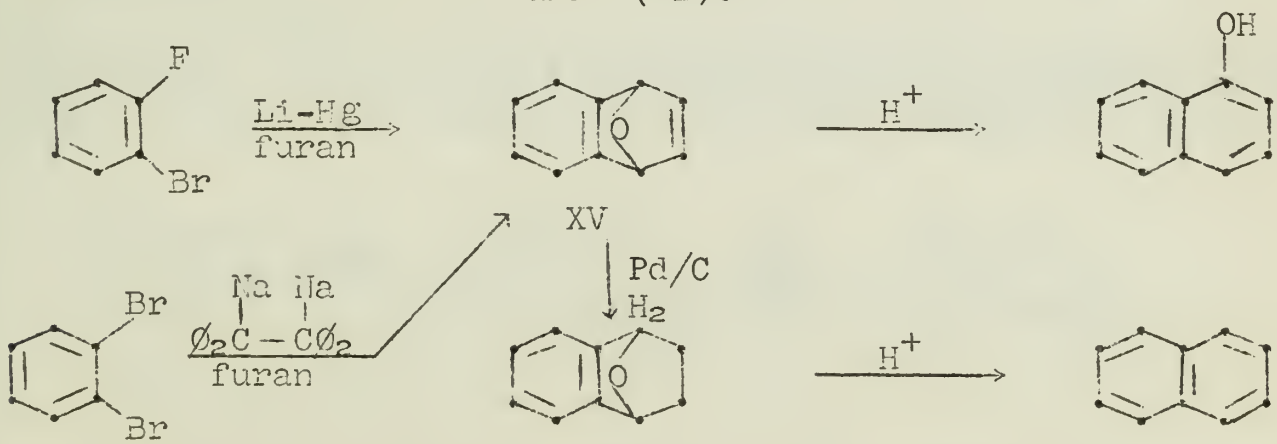
Radioactive carbon was also used by Roberts and Jenny (22) to demonstrate that the formation of biphenyl from fluorobenzene-1-^{14}C and phenyllithium proceeded <u>via</u> a benzyne intermediate as Wittig has postulated. They showed that two isomeric biphenyls were formed in the reaction by a stepwise degradation of the radioactive biphenyl.

Treatment of 1-fluoronaphthalene with phenyllithium followed by carbonation and hydrolysis of the reaction mixture gave a mixture of 1-phenyl-2-naphthoic acid (XIIa) and 2-phenyl-1-naphthoic acid (XIIb) while 2-fluoronaphthalene under identical conditions gave

3-phenyl-2-naphthoic acid (XIIc) in addition to the two products obtained before (23). These results can best be explained on the basis of formulation of both 2-naphthalyne (XIII) and 3-naphthalyne (XIV) intermediates.

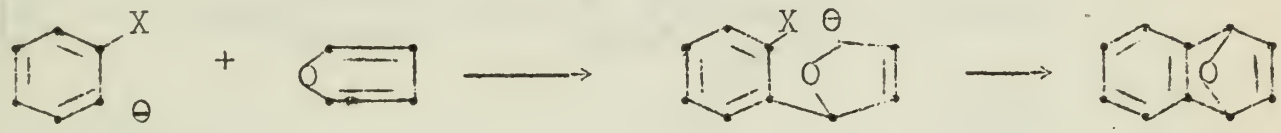


With the assumption that the benzyne intermediate had a long lifetime, Wittig and Pohmer (26) designed an experiment that would allow benzyne to function as a dienophile in the Diels-Alder reaction. Furan was chosen as the diene since it would be favorable as a solvent and would not react with lithium amalgam. Lithium amalgam was used to minimize contamination from organometallic reagents. When o-fluorobromobenzene was shaken with lithium amalgam in furan, 1,4-dihydronaphthalene-1,4-endoxide (XV) was formed. XV can also be formed from 1,2-disodium tetraphenyl ethane and o-dibromobenzene in furan (12).



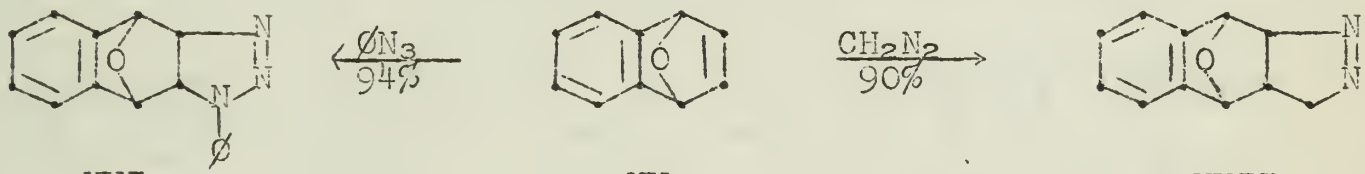
XV can be converted to α-naphthol by the use of methanolic hydrochloric acid, and, furthermore, it takes up a mole of hydrogen to give a dihydroderivative that is converted to naphthalene by

methanolic hydrochloric acid. Gilman (25) assumed that if an o-fluorophenyl anion attacked furan, the resulting compound (XVa) would not be expected to cyclize at -50° to give the highly strained endoxide (XV).



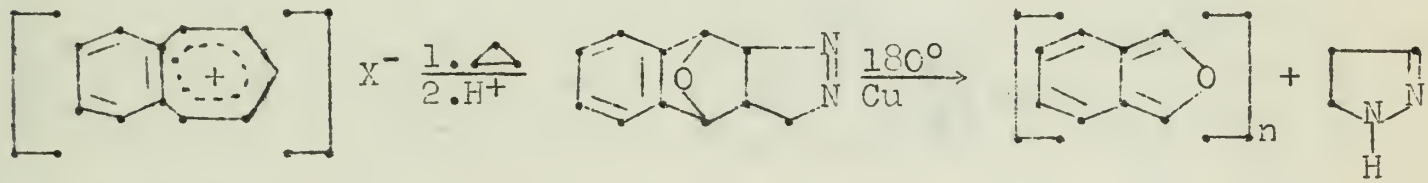
XVa XV

Gilman argues further that there is no known case where furan is attacked in such a manner and under similar conditions 2-furyllithium is the only product formed. The structure of the endoxide (XV) was confirmed by reactions with phenyl azide and diazomethane to give XVI and XVII (26, 13).



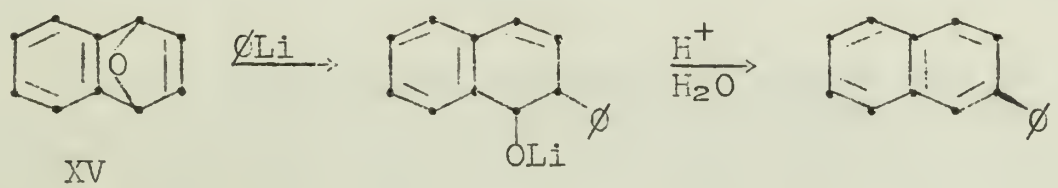
XVI XV XVII

When the pyrazoline derivative (XVII) was heated with acid, a benzotropylium salt (XVIII) was formed; decomposition with copper powder gave a polymeric 3,4-dibenzo furan (XIX) and pyrazole XX.



XVIII XVII XIX XX

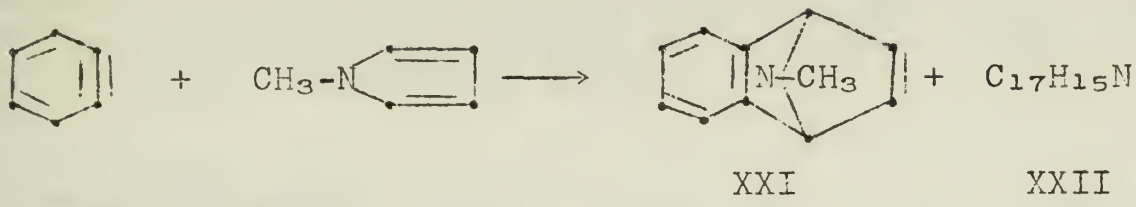
The endoxide (XV) also reacted with phenyllithium to give 2-phenylnaphthalene. This may be a feasible method of producing various β-naphthalenes which heretofore have been difficult to synthesize (13).



XV

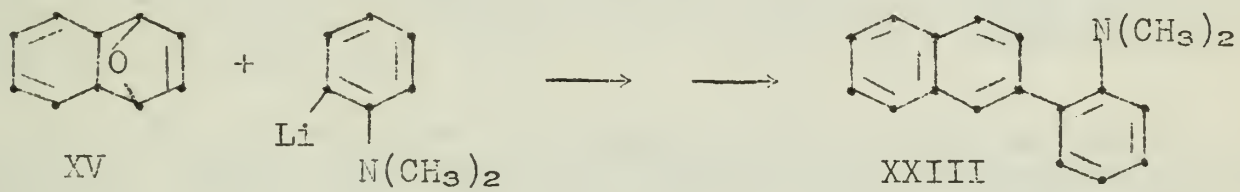
In addition to furan, cyclopentadiene, cyclohexadiene, and 1-methylpyrrole have been used as dienes (13). An interesting series of reactions occurs when 1-methylpyrrole is condensed with benzyne.

In addition to the expected product, endo-1,4-methylamino-1,4-dihydronaphthalene XXI, 18% of a new amine ($C_{17}H_{15}N$, XXII) was obtained (13).



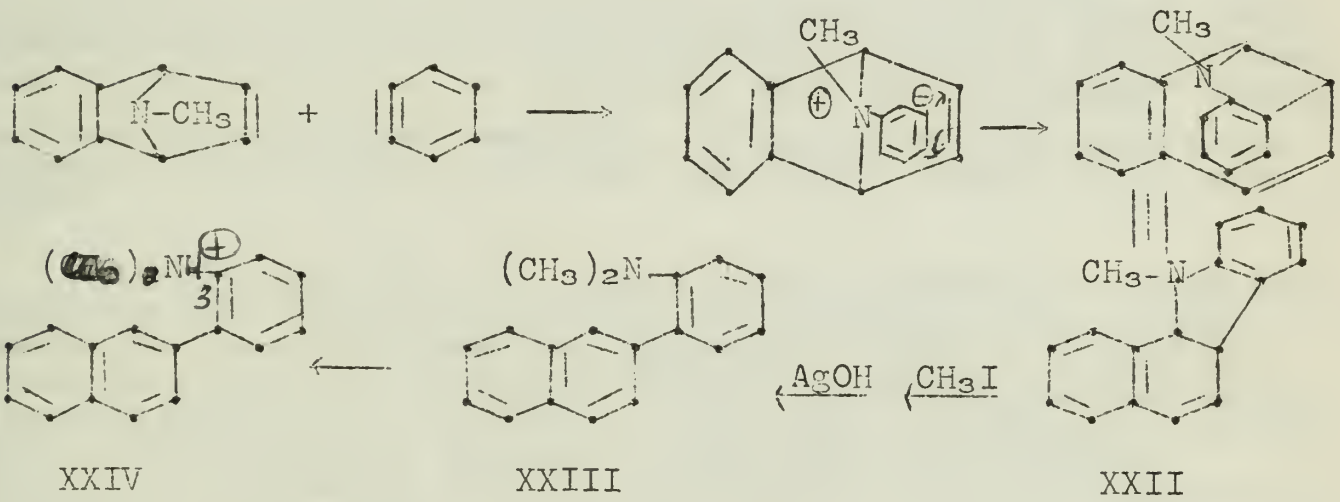
XXI XXII

Inspection of the formula seems to indicate that two moles of benzyne have condensed with one mole of amine. The unknown amine was methylated, subjected to the Hofmann reaction (XXIII), and then demethylated with hydroiodic acid to give a substituted aniline hydroiodide. Since the ultraviolet spectrum of this salt approximates the curve obtained from o-(β-naphthyl)-toluene, a reasonable guess as to its structure would be XXIV. XXIII can be synthesized by treating the endoxide (XV) with 2-dimethylamino phenyllithium



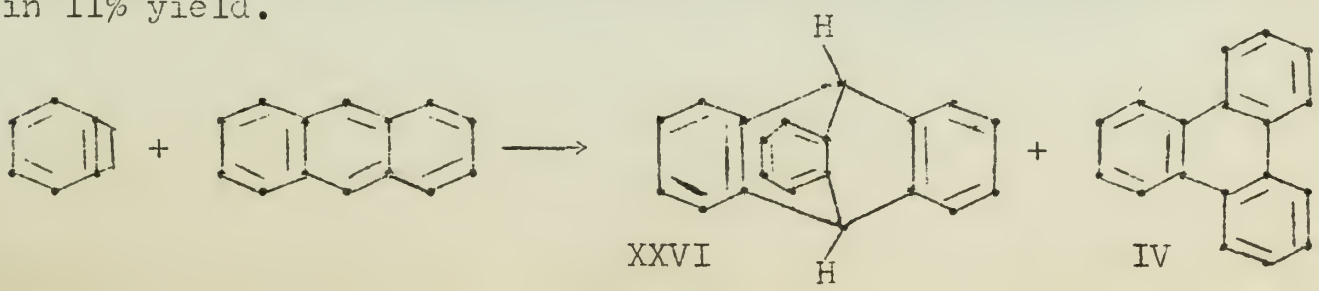
XV XXIII

The formation of XXII, XXIII, and XXIV can then be rationalized by the following sequence of reactions



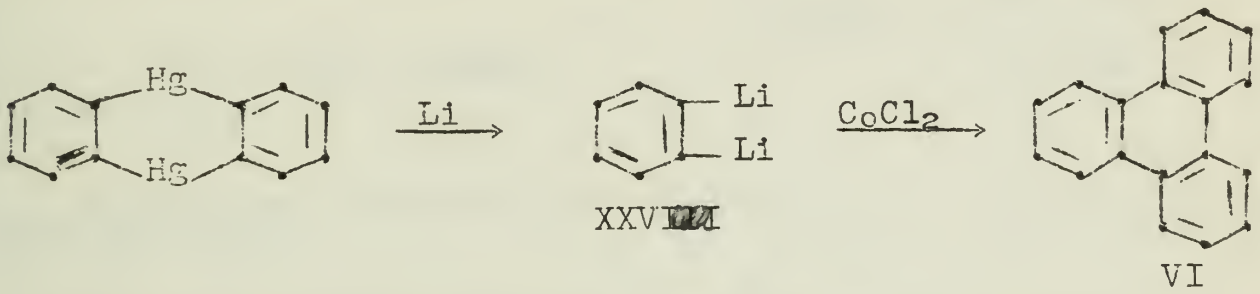
XXIV XXIII XXII

Another condensation reaction of benzyne can be realized by treating anthracene with o-fluorobromobenzene in THF (27). The benzyne intermediate adds to the 9,10 positions of anthracene to produce triptycene (XXVI) (28) in 26% yield and triphenylene (IV) in 11% yield.



XXVI IV

Wittig (13) has run several reactions under "free radical conditions" which may indicate the existance of a "benzyne diradical". If dimercura-9,10-dehydro anthracene is treated with lithium in ether, O-dilithium benzene (XXVII) is obtained. Treatment of the dimetalated benzene with 2-5 mole percent of cobalt II chloride gave triphenylene (VI).

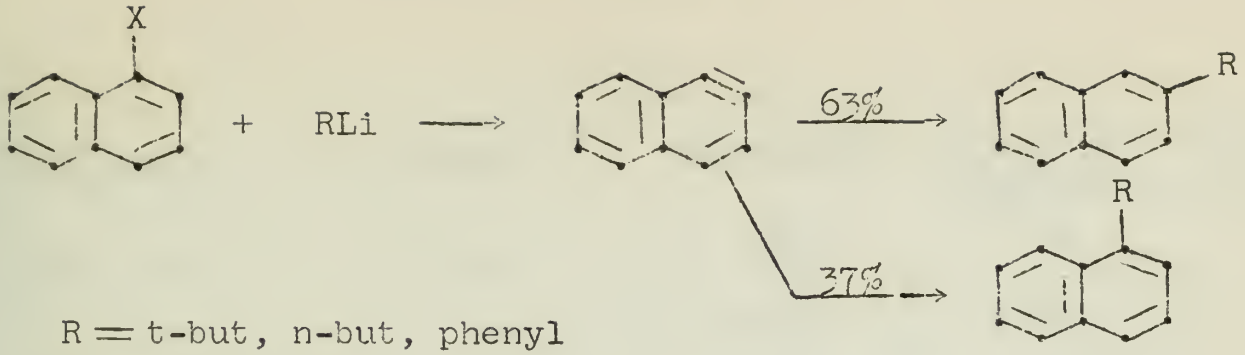


XXVII VI

When this reaction was run in the presence of furan no endoxide was formed. Wittig concluded that these observations indicate that a triplet state of benzyne may be formed, however, this is not a convincing argument since the reaction could proceed either via an ordinary displacement reaction or via a benzyne mechanism if the rate of coupling of benzyne with itself is greater than condensation with furan.

In 1946, it was noted that meta cresols could be formed in good yields if ortho- and para-halo toluenes were treated with sodium hydroxide at 300° (30). Treatment of chlorobenzene with sodium hydroxide produced a variety of products including 2,6-diphenyl phenol, p-phenoxydiphenyl, and hydroxydiphenyls (31). The mode of formation of all these products can easily be explained in terms of a benzyne intermediate. Roberts has presented evidence for a benzyne mechanism (21) in these reactions. However, he has shown that a direct substitution mechanism (S_N2) may predominate depending upon the conditions employed. It was noted that even under optimum "benzyne type" conditions some direct substitution seems to occur.

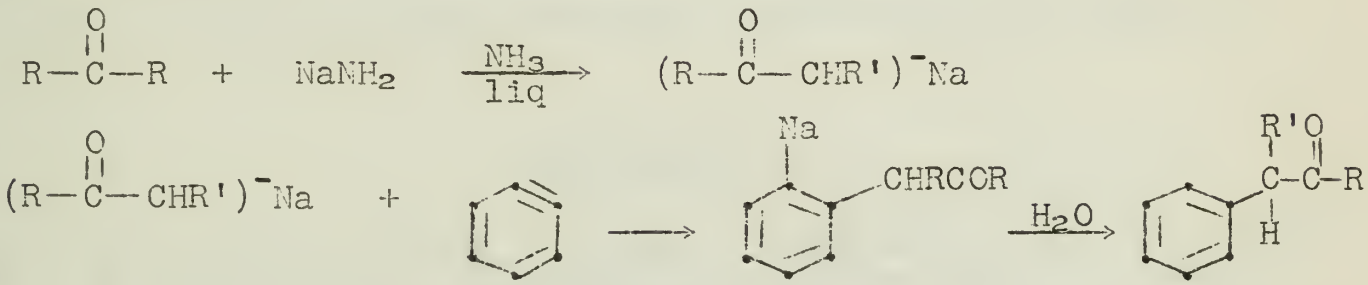
Huisgen et.al. (33, 34) used lithium piperidide in piperidine in reactions with 1-fluoronaphthalene and found that the relative amounts of 1 and 2-N-piperidyl naphthalene could be varied by controlling the mole ratios of lithium piperidide and piperidine. A benzyne mechanism is favored at high amide concentration while a direct substitution is favored at high amine concentration. Bunnett and Brotherton (35, 36, 37) have reacted halobenzenes with sodamide in the presence of various secondary amines and have synthesized N-aryl piperidines and dialkylanilines in good yields. Huisgen and Zirngebl (42) reacted 1-halonaphthalenes with t-butyllithium, n-butyllithium and phenyllithium and observed that neither the stability of the carbanions nor their steric requirement influenced the ratio of 1- or 2-substituted naphthalenes.



R = t-but, n-but, phenyl

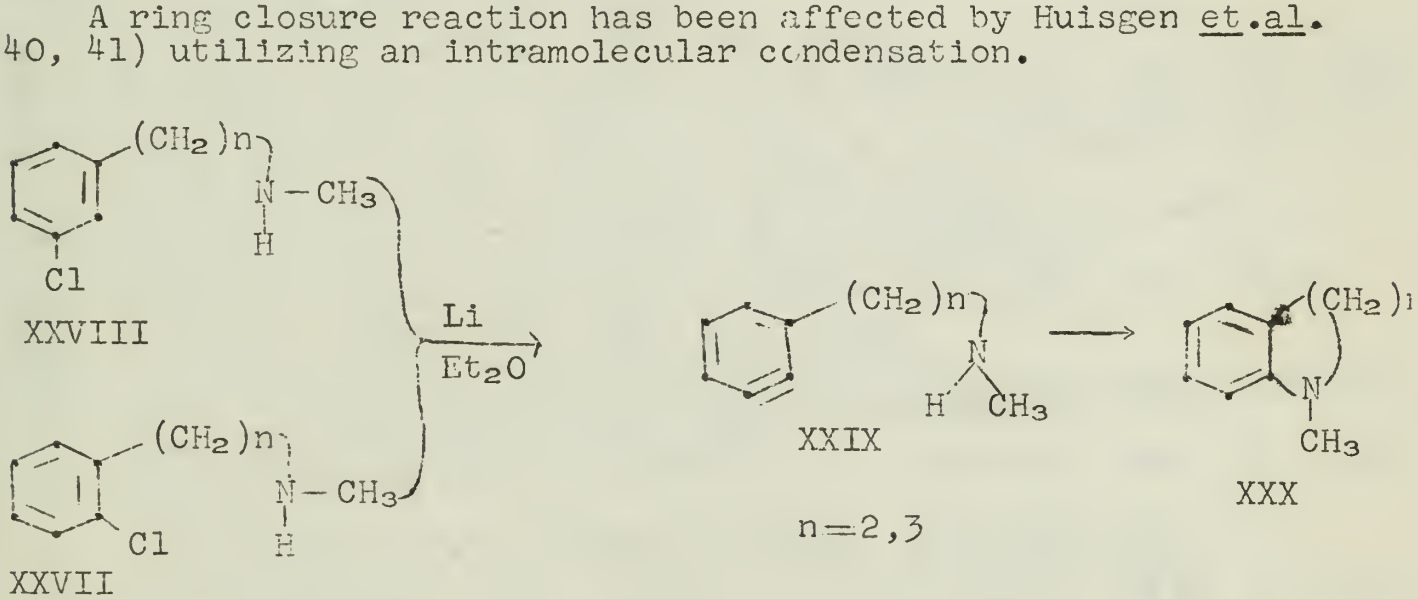
X = F, Cl.

Alpha-phenyl ketones can be synthesized in good yields in the following manner.



Simple esters, mercaptans, nitriles, acetylenes, and tar bases can be phenylated via a benzyne intermediate in fair to good yields (39). Malonic ester can be phenylated in 51% yield under the same conditions.

A ring closure reaction has been affected by Huisgen et.al. (40, 41) utilizing an intramolecular condensation.



The reaction may proceed either by the replacement of lithium for the hydrogen in the secondary amine followed by cyclization and elimination of lithium chloride, or it may go by replacement of the hydrogen by lithium at the ortho position, thereby forming the benzyne intermediate XXIX. The former reaction seems to be favored as indicated by the data in table 2; since XXVII always gives better

TABLE 2

Sec. amine	Product	Yield XXX	% Starting Material	% Reduction of Halide
XXVII n=2	XXX n=2	58%	0	0
n=3	n=3	28%	13	4
XXVIII n=2	n=2	35%	23	0
n=3	n=3	7%	59	11

yields of XXX than XXVIII provided the ring size is constant.

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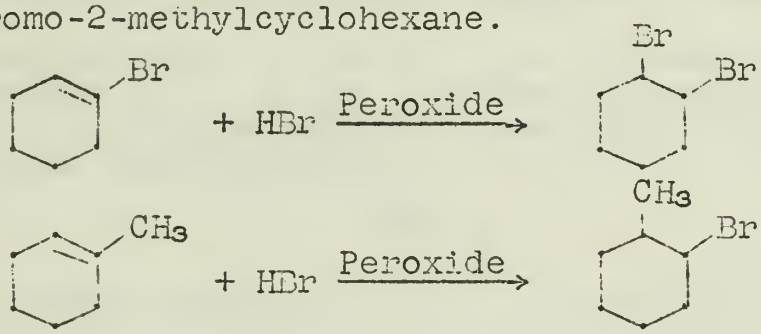
THE STEREOCHEMISTRY OF FREE RADICAL ADDITIONS TO OLEFINS

Reported by G. F. Fanta October 21, 1957

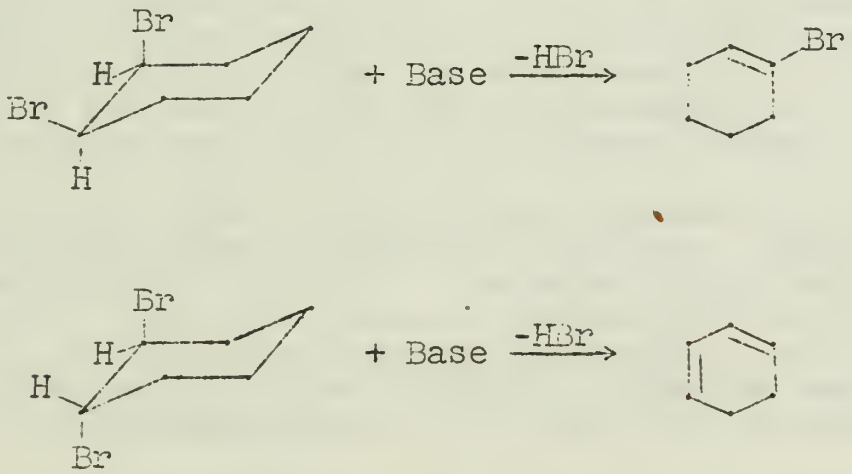
This seminar will cover addition of free radicals to olefinic compounds only and will include a brief discussion of some of the radical intermediates which have been proposed. Free radical additions to aromatic compounds and acetylenes will not be discussed.

The first investigation concerning the stereochemistry of free radical addition to the cyclohexene ring involved the addition of hydrogen bromide to 1-bromocyclohexene and 1-methylclohexene (1). Under free radical conditions, the expected adduct from 1-bromocyclohexene would be 1,2-dibromocyclohexane and that from 1-methylcyclohexene would be 1-bromo-2-methylcyclohexane.



In the cyclohexene system, cis - trans isomerizations of the double bond do not occur. Therefore, one may deduce the stereochemistry of the addition by observing the configuration of the addition products.

By assuming trans elimination to be required in base promoted dehydrobrominations (2), cis-1,2-dibromocyclohexane should be converted to 1-bromocyclohexene by dehydrobromination, whereas the trans isomer has been shown to be primarily converted to cyclohexadiene (3).



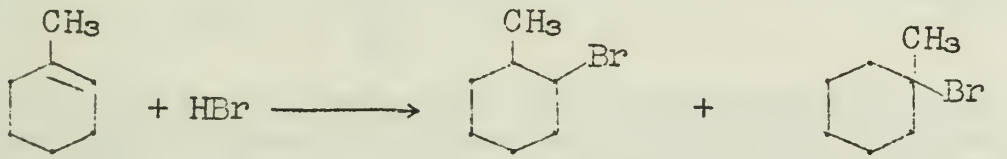
Similarly, 1-methylcyclohexene would be expected from the dehydrobromination of cis-1-bromo-2-methylcyclohexane, and 3-methylcyclohexene from the trans isomer.

The addition of hydrogen bromide to 1-bromocyclohexene was found to proceed rapidly when catalyzed by benzoyl peroxide or ultraviolet light but does not occur in the presence of inhibitors of free radical

additions such as hydroquinone (1). Under ionic conditions, in the presence of diphenylamine or a ferric chloride-diphenylamine mixture, nearly all the 1-bromocyclohexene was recovered indicating ionic addition to be extremely slow.

The addition product isolated from the free radical addition had the correct analysis for dibromocyclohexane and depressed the melting point of trans-1,2-dibromocyclohexane. When dehydrobrominated in alcoholic potassium hydroxide, 1-bromocyclohexene was isolated in 78% yield. The 1,1-isomer would be expected to hydrolyze readily to cyclohexanone; but when the addition product was heated for eleven hours with water, no material was produced which would give a carbonyl test with 2,4-dinitrophenylhydrazine. Because of this evidence the addition product was assumed to be the cis compound.

1-Methylcyclohexene undergoes ionic addition more rapidly than 1-bromocyclohexene (1). In the presence of benzoyl peroxide or ultraviolet light, 1-bromo-1-methylcyclohexane and 1-bromo-2-methylcyclohexane are formed simultaneously.



(ca. 75%) (ca. 25%)

The composition of the addition product was determined by selective hydrolysis of the teritiary bromide in 80% aqueous acetone at 100° (1).

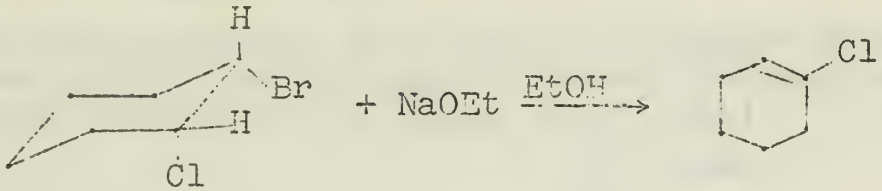
Since 1-bromo-1-methylcyclohexane is formed exclusively under ionic conditions, 1-bromo-2-methylcyclohexane must result from free radical addition. In the presence of benzoyl peroxide, ionic addition occurs exclusively at -80°; however, increasing the temperature causes free radical addition to predominate. Since the conversion of a secondary to a tertiary bromide may occur readily in the presence of hydrogen bromide (5), a pentane solution of the addition product of known composition was subjected to the conditions of the reaction. Because this addition product was recovered unchanged, it appears that the products isolated are the initial products formed.

The addition product of hydrogen bromide and 1-methylcyclohexene, when dehydrobrominated in anhydrous pyridine, yielded 1-methylcyclohexene almost exclusively (1). Assuming trans dehydrobromination, this indicates that the 1-bromo-2-methylcyclohexane obtained is the cis isomer. To show that 1-methylcyclohexene was the initial product of dehydrobromination, pure 3-methylcyclohexene was submitted to the conditions of the reaction and was recovered unchanged in 91% yield.

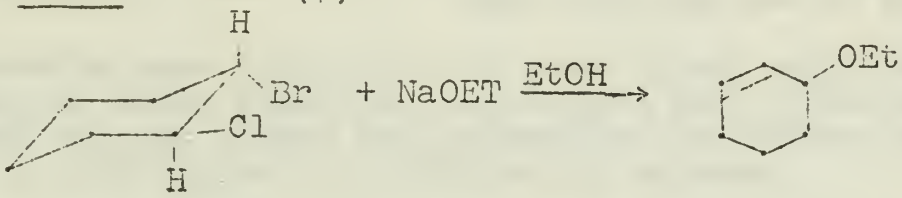
The addition of hydrogen bromide to 1-chlorocyclohexene proceeds rapidly when the mixture is irradiated with ultraviolet light and gives cis-1-bromo-2-chlorocyclohexane (6).

Since addition does not occur in the absence of radiation, a free radical mechanism is involved.

The structure of cis-1-bromo-2-chlorocyclohexane was proved by refluxing with sodium ethoxide in ethanol (6). The following reaction took place:

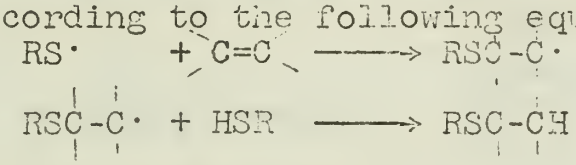


If trans elimination is assumed, 1-chlorocyclohexene could only result from the cis isomer. This is supported by the following reaction (6) observed for the trans isomer (7):

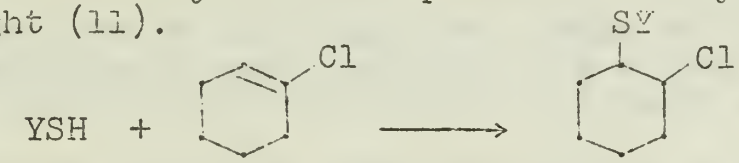


Also, a comparison of physical properties and infrared spectrum with those of trans-1-bromo-2-chlorocyclohexane and 1-bromo-1-chlorocyclohexane showed that the addition product was neither of these compounds.

It has been shown that sulfhydryl compounds undergo radical additions to alkenes according to the following equations (8,9,10):

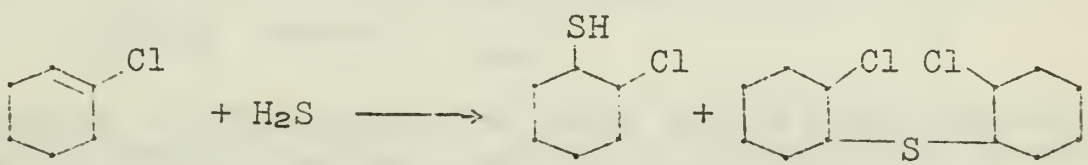


The radical additions of hydrogen sulfide, thiophenol, and thioacetic acid to 1-chlorocyclohexene proceed readily when initiated by ultraviolet light (11).



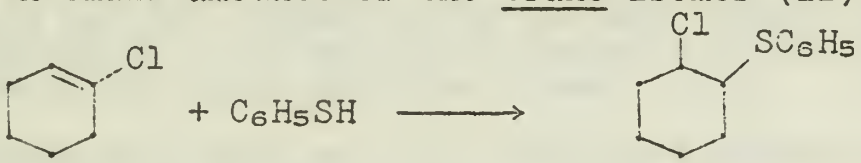
Since the reactivity of the trans isomer in solvolysis reactions is much greater than that of the cis, the composition of a mixture of cis and trans isomers was determined by selective solvolysis of the trans isomer. The solvolysis conditions for each addition product will be discussed below.

The radical addition of hydrogen sulfide to 1-chlorocyclohexene resulted in the formation of 2-chlorocyclohexanethiol together with a high boiling residue which appeared to be bis-2-chlorocyclohexyl sulfide (11).



Selective solvolysis was carried out in 80% ethanol at 100° for 45 minutes. Under these conditions, pure trans-2-chlorocyclohexanethiol releases one equivalent of chloride ion, while the cis isomer releases less than .002 equivalent (11). It was shown by this method that the 2-chlorocyclohexanethiol formed in this reaction consisted of about 85% cis and 15% of the trans isomer.

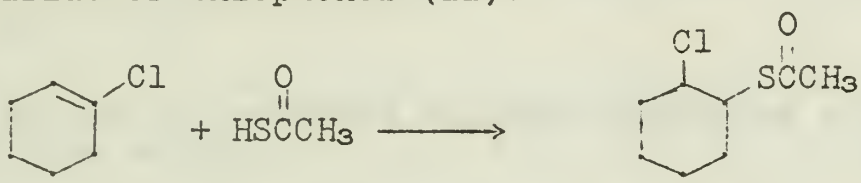
The addition of thiophenol to 1-chlorocyclohexene under free radical conditions gave primarily cis-2-chlorocyclohexylphenyl sulfide together with small amounts of the trans isomer (11).



(ca. 95% cis and 5% trans)

The addition products were identified as pure binary mixtures of cis and trans isomers by their chemical composition and infrared spectra, and the percentage of cis isomer was determined as before by selective solvolysis in 80% ethanol at 100° for 45 minutes.

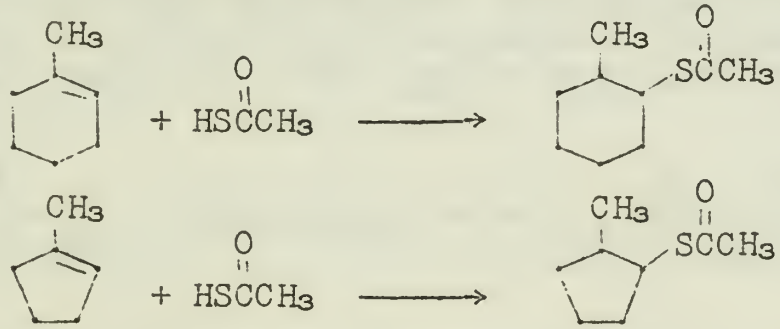
For the free radical addition of thioacetic acid to 1-chlorocyclohexene, the addition product was found to contain a higher percentage of trans isomer than was obtained in the addition of hydrogen sulfide or thiophenol (11).



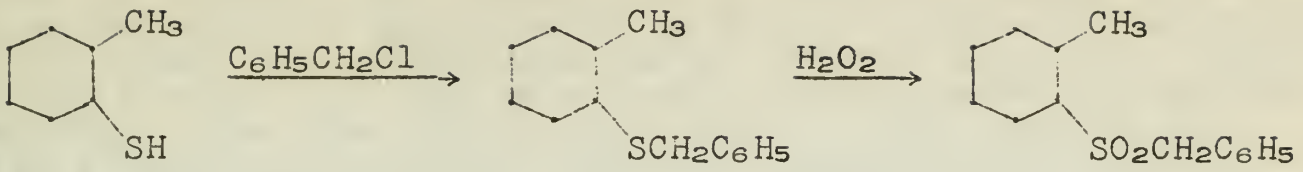
(ca. 70% cis and 30% trans)

The infrared spectrum of the adduct was found to be a composite of the spectra of pure cis and trans isomers. The amount of trans isomer was determined by selective solvolysis in ethanol at 50° for 48 hours.

When catalyzed by light, excellent yields of thioacetates were obtained from the reactions between 1-methylcyclohexene and thioacetic acid and 1-methylcyclopentene and thioacetic acid (12).

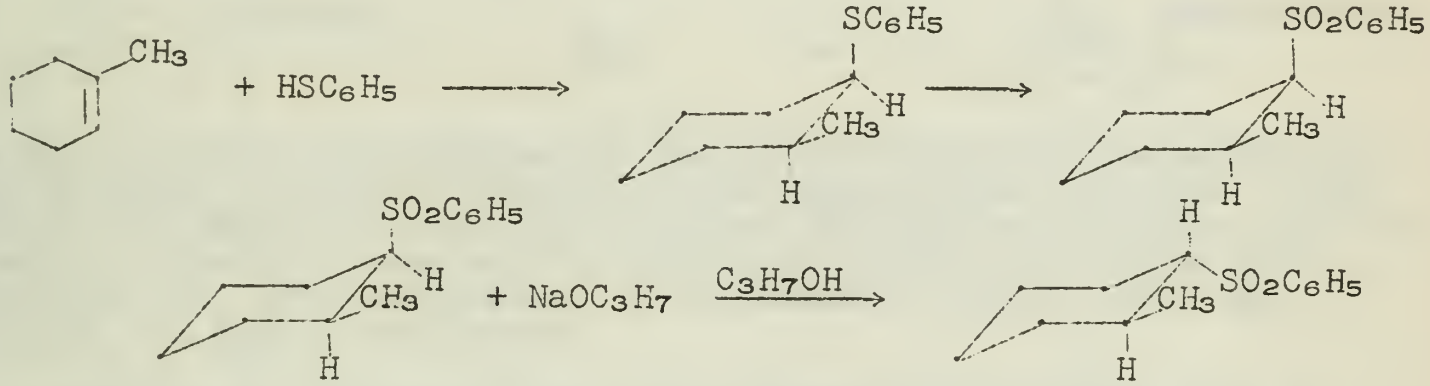


These were hydrolyzed to the thiols, the crude thiols were converted to the corresponding benzyl sulfides, and these were oxidized to the sulfones which were purified by fractional crystalization.



In each case the sulfone formed could be isomerized almost completely by heating with sodium propoxide in n-propyl alcohol. From this evidence, it was concluded that the original sulfone had mainly the cis structure and was isomerized to the more stable trans isomer on heating with alkali. Further study showed that the cis compound made up about 80% of the total addition product (12).

Thiophenol will also add to 1-methylcyclohexene by trans addition (12). The reactions involved are as follows:

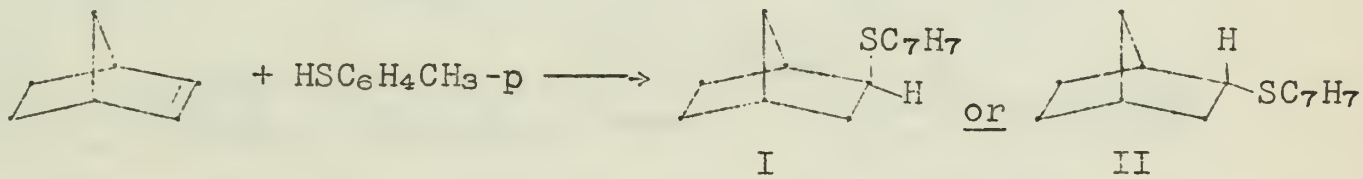


The isomerization in the above equation indicates a cis configuration for the original sulfone.

The radical additions of hydrogen sulfide, thiophenol, and thioacetic acid are not as stereospecific as the reaction with hydrogen bromide. However, in every case, trans addition predominates (11). The stereospecificity of the addition has been found to decrease in the order:

$$C_6H_5SH > H_2S > CH_3\overset{O}{\overset{\|}{C}}SH$$

The stereochemistry of free radical additions to some bicyclic systems has also been determined. The products of the addition of p-thiocresol to bicyclo-(2,2,1)-heptene-2 (norbornylene) without rearrangement might be either exo-or endo-norbornyl-p-tolyl thioether.



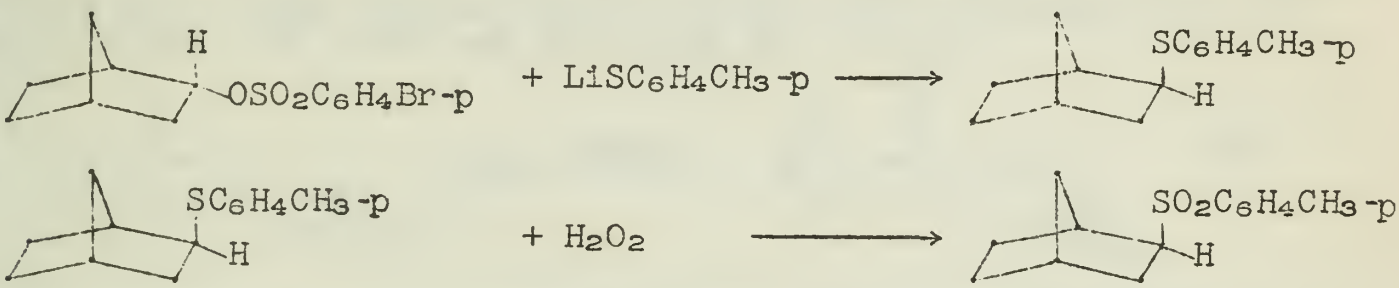
I II

A rearrangement product analogous to the product of a Wagner-Meerwein rearrangement (13) in an ionic addition would be 7-p-thiocresoxynorcamphane (III).

III

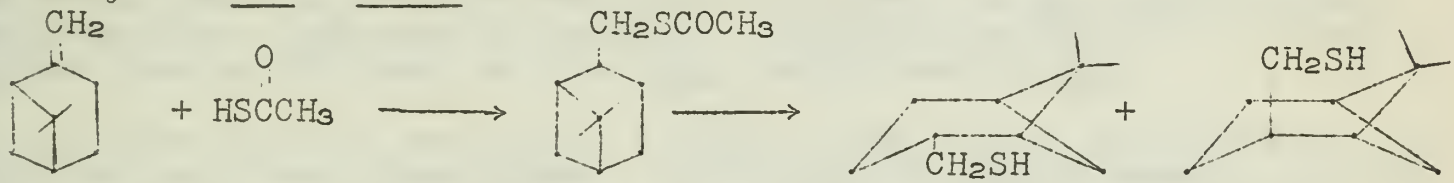
When norbornylene was treated with an equimolar amount of p-thiocresol, an 85% yield of exo-norbornyl-p-tolyl thioether (I) was obtained (14). The product of the reaction did not contain significant amounts of the endo product (II), and there was no rearrangement to compounds of type (III). The free radical chain nature of the reaction was proved by studying the effect of peroxide catalysts and inhibitors upon the rate of reaction.

Evidence for the exo configuration involves the displacement reaction with lithium-p-thiocresoxide on endo-norbornyl-p-bromobenzene sulfonate and the subsequent oxidation with hydrogen peroxide. (14)

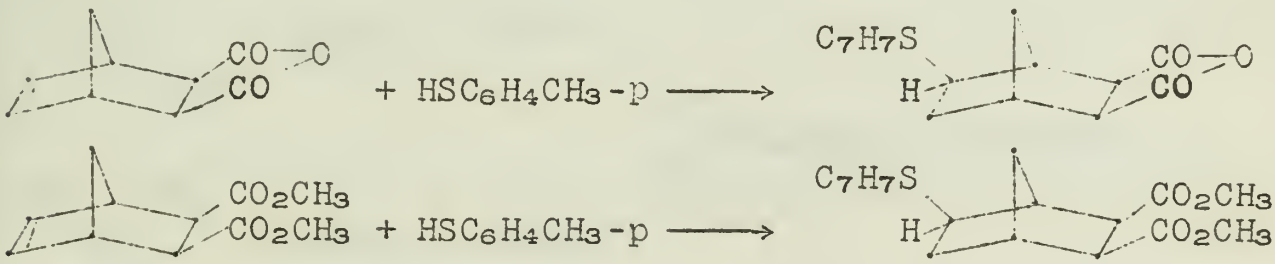


The exo structure was assigned to the above sulfone on the assumption that a Walden inversion occurred in the displacement reaction. This sulfone was identical with that produced from the norbornylene addition product. Identical treatment of the exo-norbornyl-p-bromobenzene sulfonate led, after oxidation, to an isomeric sulfone which was assigned the endo-configuration.

Addition of thioacetic acid to β-pinene and hydrolysis gave a mixture of two thiols (12). By infrared analysis of the 2,4-dinitrophenyl sulfide derivatives it was concluded that no rearrangement of the carbon skeleton had taken place. The two thiols formed are probably the cis - trans isomers shown below.



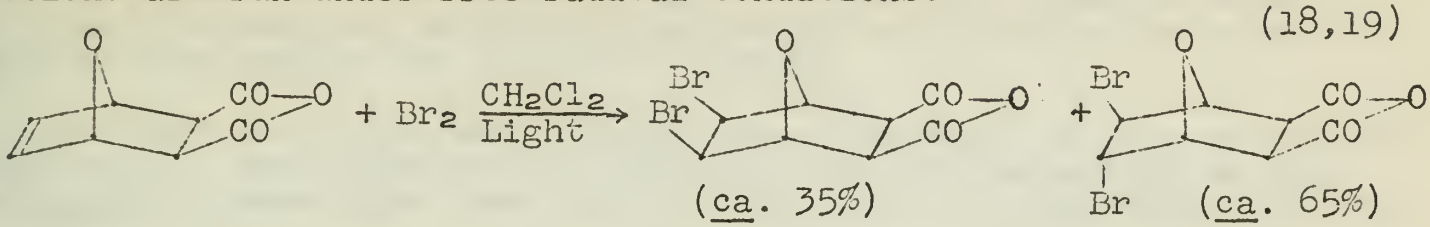
On investigating further the addition of p-thiocresol to bicyclic olefins, the following reactions were found to occur (15).



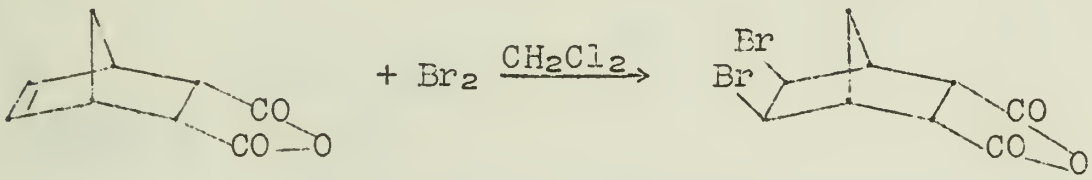
No rearrangement was observed. The exo-configuration of the C_7H_7S groups was assigned on the basis of Alder's exo- addition rule (16,17) and also by analogy to the norbornylene adduct, the stereochemistry of which was demonstrated (14).

The following reactions of bicyclic olefins with bromine are interesting in that the bromine appears to add in a cis manner when the reactions are run under free radical conditions.

(18,19)

1.) 

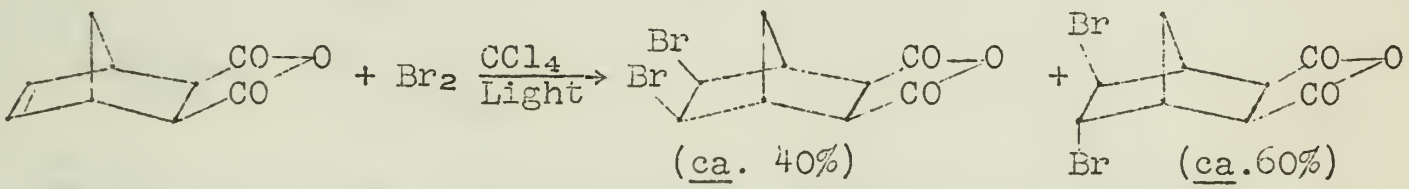
When the above reaction was run in darkness, the yield was 81% trans and 9.7% cis. When run in a polar solvent such as acetic acid or ethyl acetate, the yield was 90% trans and 0% cis.

2.) 

(18)

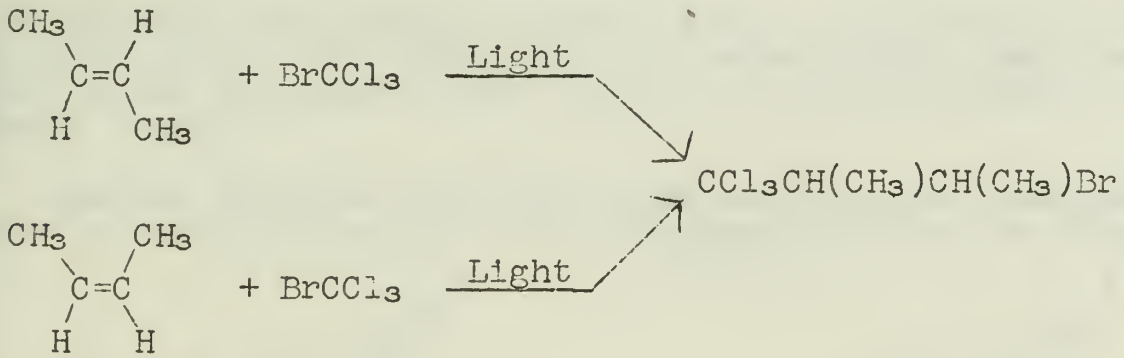
The above reaction appeared to be light catalyzed. There was no mention of the isolation of any trans isomer. When run in acetic acid or ethyl acetate, a complex mixture of products was obtained some of which was the cis isomer. The percentage composition of this mixture was not specified.

(20)

3.) 

The above reaction was very sensitive to light and cis addition was suppressed or eliminated by darkness. Running the reaction in ethyl acetate gave a 92% yield of the trans isomer and 0% cis.

In the field of non-cyclic olefins, free radical additions to 2-butene have been investigated. Both cis and trans-2-butene produced the same mixture of diastereomers when reacted with bromotrichloromethane (21).

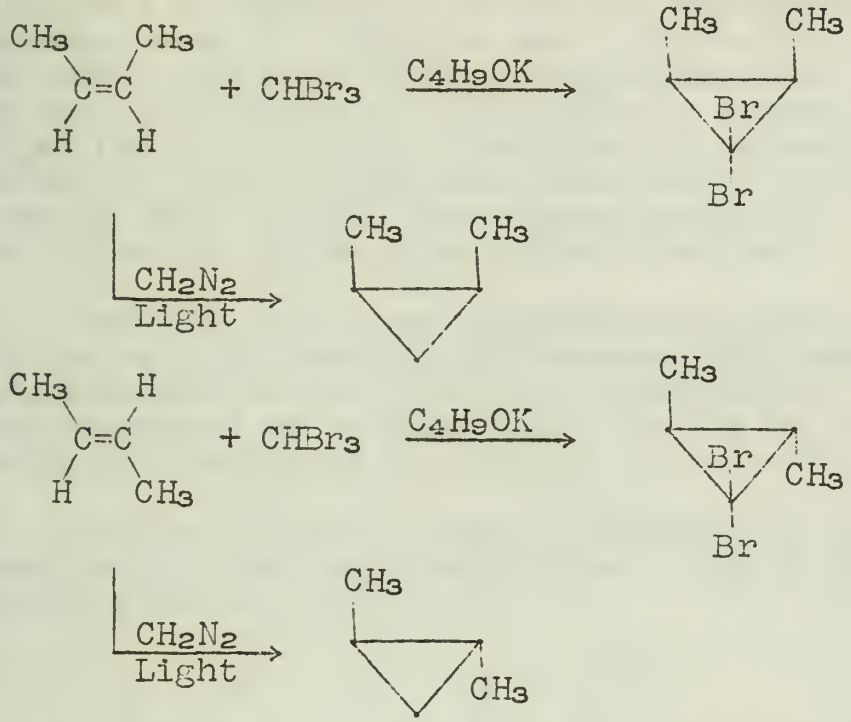


The photochemical addition of benzenesulfonyl iodide to cis and trans-2-butene was also shown to lead to the same mixture in both instances (31).

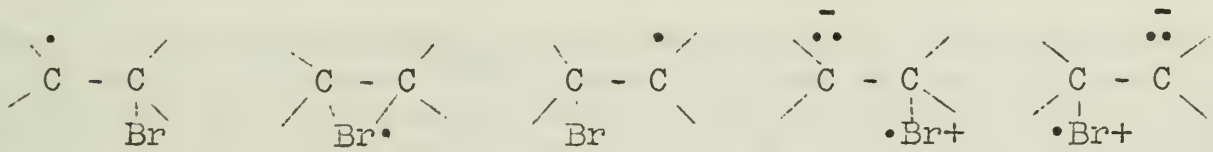
$$CH_3CH{=}CHCH_3 + C_6H_5SO_2I \xrightarrow{\text{Light}} C_6H_5SO_2CH(CH_3)\text{-}CH(CH_3)I.$$

The infrared spectra of the two mixtures were identical, and identical quantities of one of the isomers (it was not reported which isomer) could be separated from either mixture. These two examples indicate that the intermediate radical is completely equilibrated among all its conformations before the product is formed.

Carbenes have also been studied from the point of view of stereospecificity. The additions of methylene and dibromocarbene to cis- and trans-2-butene have been found to proceed in a cis manner (23,24).

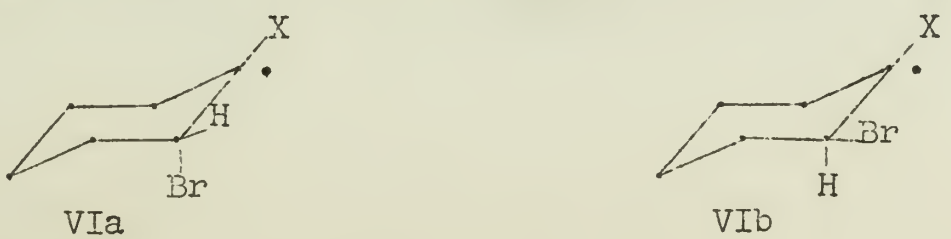


To account for the observed trans addition in the cyclohexene series, Goering has proposed that the bromine atom may be centrally located between the carbon atoms thus permitting stabilization of the radical by the following contributing structures (1).



If we consider this hybrid radical which is analagous to the bromonium ion involved in ionic additions, it seems likely that the hydrogen would become attached to the carbon on the side opposite from the bromine bridge.

Another possible structure proposed for the intermediate radical which is consistent with preferred trans addition is (VIa) (6).



VIa VIb

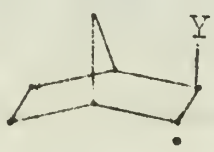
If the radical has this conformation, there is steric advantage for hydrogen bromide to approach the radical from the side away from the axial bromide. Structure (VIa) was previously considered unlikely, for it was assumed that the radical would exist in a form in which the bromine atom was equatorial (VIb). However, it has been pointed out that although (VIb) is sterically less strained than (VIa), the carbon-halogen bonds in (VIb) are nearly coplaner. This form is thus destabilized by electrostatic interaction between the halogen atoms (30). Because the electrostatic and steric effects oppose each other, it is difficult to say which of the two structures has greater stability. However, even if (VIb) is more stable than (VIa), it seems likely that the chain carrying radical approaches the double bond perpendicular to the nodal plane of the ethylenic linkage causing the formation of (VIa) (25). If (VIa) undergoes the transfer step before being converted to (VIb), trans addition would be expected. Therefore, according to this theory, the stereospecificity of the addition depends on the lifetime of the intermediate radical.

The fact that some cis addition occurs in the addition of thioacetic acid to 1-methylcyclohexene (12) shows that the bridged radical intermediate is not entirely satisfactory. The bridged radical theory is also shown to be inadequate by the failure of radical additions to occur by stereoselective paths in non-cyclic alkenes (21,22).

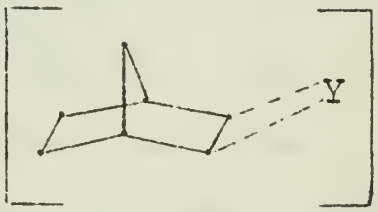
In the field of bicyclic olefins of the norbornylene type, we usually picture ionic additions as going through an intermediate cation such as (VII) (13).

VII

VIII



IX



X

However, since rearrangements are consistently observed not to occur, the analogous structure (VIII) does not seem to be involved in additions of the free radical type. The possibility of a bridged radical such as (X) is unlikely due to the discovery of cis addition of bromine under free radical conditions. Therefore, the data available at present seems to favor the classical structure (IX).

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RECENT ADVANCES IN TRANSANNULAR REACTIONS

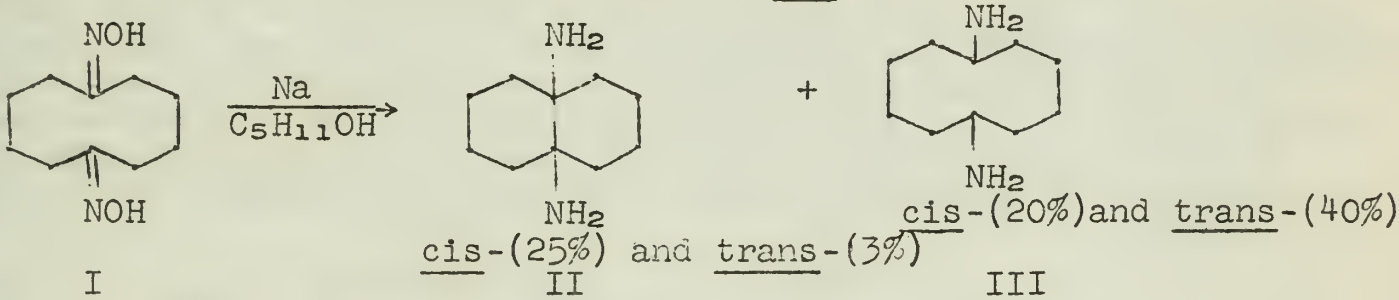
Reported by A. G. Cook October 24, 1957

INTRODUCTION

Transannular reactions have been defined as reactions occurring between nonadjacent ring atoms in cyclic compounds (1). Such reactions have been covered in two previous seminars (1,2); accordingly, the present seminar will deal primarily with the more recent advances in this field. Discussion of transannular nitrogen-carbonyl interactions, reviewed by Leonard (3), will be omitted, as will interactions of any other type (4). Transannular interactions refer to the formation of a partial bond or to a field effect across the ring as opposed to the formation of a full bond. Transannular reactions may involve the formation of a full bond across the ring or a hydride shift across the ring. Transannular reactions generally occur in medium-sized rings (8 to 12 members). The geometric conformations of the rings brings the groups on opposite sides of the ring into close proximity, hence facilitating transannular reactions.

TRANSANNULAR RING CLOSURES

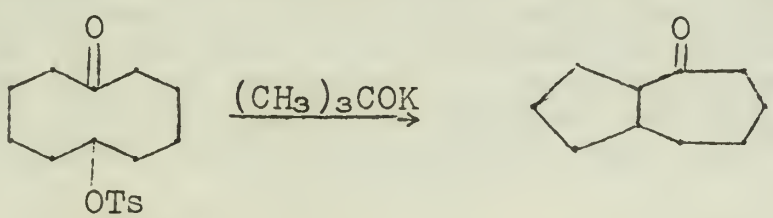
In 1944 Plattner and Hulstkamp (5) isolated the transannular products cis- and trans-9,10-diaminodecalin (II) as well as the "normal" cis- and trans-1,6-diamino-cyclodecane (III) when cyclodecane-1,6-dione dioxime (I) was reduced with sodium and amyl alcohol. A similar transannular product, cis-9,10-dihydroxydecalin,



cis-(25%) and trans-(3%) cis-(20%)and trans-(40%)

I II III

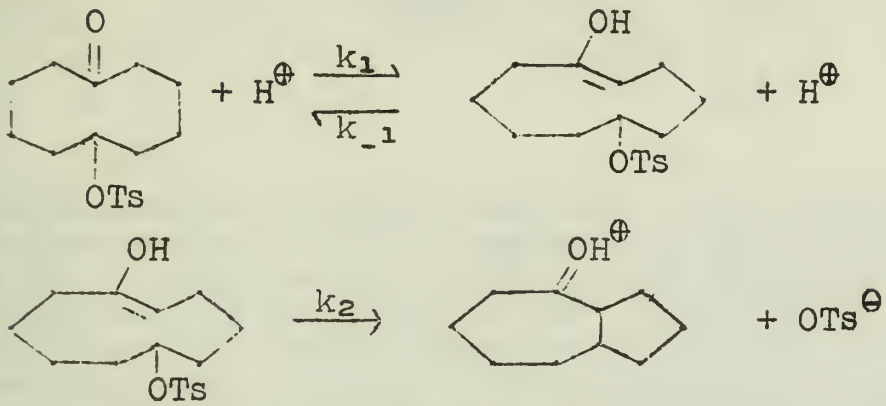
was obtained as the minor product in the catalytic reduction of 1,6-cyclodecanone (6). Since this time many other examples of transannular ring closures have been found (1,2). For instance, Cope (7) found that when 6-ketocyclodecyl tosylate (IV) was treated with potassium t-butoxide, bicyclo [5 .3.0]decan-2-one (V) resulted as a stereoisomeric mixture (66% yield). Recently Goering (8) has investigated the solvolysis of 6-ketocyclodecyl tosylate (IV) and brosylate with



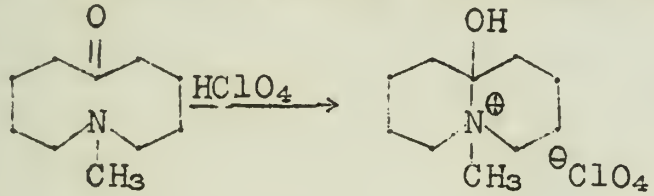
IV V

absolute ethanol and has found that pure bicyclo [5.3.0]decan-2-one (V) was obtained in an 88% yield. Its stereoisomeric composition was almost identical to that found in Cope's reaction. Apparently the product resulted from thermodynamic control: the trans isomer predominated in a ratio of 3-4:1. The ethanolysis of IV was acid catalyzed and hence was autocatalytic. Rate studies indicated that

the reaction involved a second order, reversible enolization followed by a first order conversion of the enol to the product as follows:



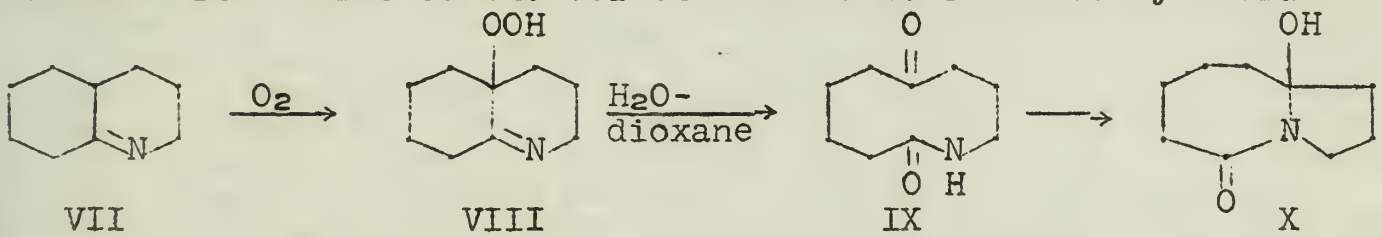
Transannular interactions have been observed in eight, nine, and ten membered rings which possess a teritiary amine group opposite a carbonyl group (3). Moreover, these same compounds show a transannular reaction when their corresponding salts are made (9), e.g., formation of VI. Cohen and Witkop (10) have demonstrated that an amide nitrogen



(6 μ region transparent)

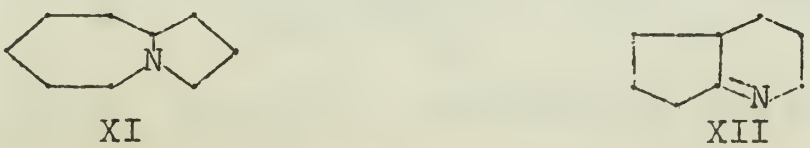
VI

can react with a ketone across a ten-membered ring. $\Delta^{1(9)}$-Octahydroquinoline (VII) was oxidized to 10-hydroperoxy-$\Delta^{1(9)}$-octahydroquinoline (VIII). When 10-hydroperoxy-$\Delta^{1(9)}$-octahydroquinoline (VIII) was allowed to stand in a water-dioxane mixture (1:1) at 25°, 7-hydroxy-2-keto-1-azabicyclo[5.3.0]decane (X) was produced as the exclusive product. The course of the reaction could be followed by infrared.



VII VIII IX X

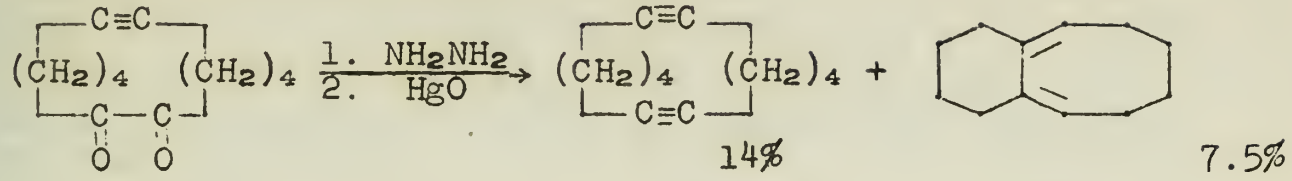
The rate of formation of the keto-lactam (IX) and the rate of the transannular reaction of -NH with the ketone were both increased by increasing the acid strength of the solution. When X was hydrogenated with platinum in hydrochloric acid the hydroxyl group was lost. When it was reduced with lithium aluminum hydride, 1-azabicyclo-[5.3.0] decane (XI) was produced. In neither case, however, was an open keto-lactam reduction product obtained. An analogous transannular reaction was observed in the 9-membered ring, $\Delta^{1(8)}$-hexahydro-1-pyridene (XII).



XI XII

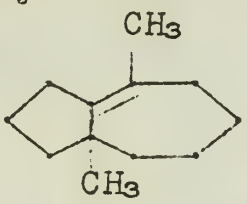
Cram (11) while synthesizing 1,7-cyclododecadiyne (XIV) by oxidation of the hydrazone of 7,8-diketocyclo-dodecyne (XIII) with mercuric oxide obtained a second product as the result of a transannular reaction

1,7-[6.4.0]-bicyclododecadiene (XV).



XIII XIV XV

The transannular reaction could well have followed a Wolff-Kishner reduction sequence. This supposition was fortified by the observation that when a small amount of potassium hydroxide was added to the reaction mixture the yield of the transannular product (XV) was raised from 7.5% to 12%, whereas the yield of the diyne (XIV) was reduced to zero. Again in the ten-membered ring series, Prelog (12) observed that when either cis- or trans-1,6-dimethyl-1,6-cyclodecanediol was allowed to react with 84% phosphoric acid, the same $C_{12}H_{20}$ hydrocarbon was obtained. This hydrocarbon took up one mole of hydrogen upon catalytic hydrogenation with platinum and was therefore a bicyclic compound, probably XVI.



XVI

TRANSANNULAR HYDRIDE SHIFTS

Cope (13) and Prelog (14,15,16,17) have shown previously that treatment of 8- through 11-membered ring olefins with performic acid, followed by hydrolysis, yielded some diols indicative of transannular reaction having taken place. For example, Cope (13) found that treatment with performic acid and hydrolysis of cis-cyclooctene resulted in a 22% yield of trans-1,2-cyclooctanediol and a 26% yield of 1,4-cyclooctanediol of unknown configuration (but a single stereoisomer). A consideration of the probable mechanism, namely a double Walden inversion for the transannular diol formation, would lead one to the conclusion that the 1,4-cyclooctanediol is cis. The reaction is very likely a concerted reaction, since it is stereospecific. The performic acid first forms the protonated epoxide ring, and then the transannular reaction takes place upon hydrolysis. This involves a hydride shift induced by a rearward attack by the solvent and a simultaneous opening of the protonated epoxide ring. Prelog's work with cyclodecene tended to support this mechanism (14).

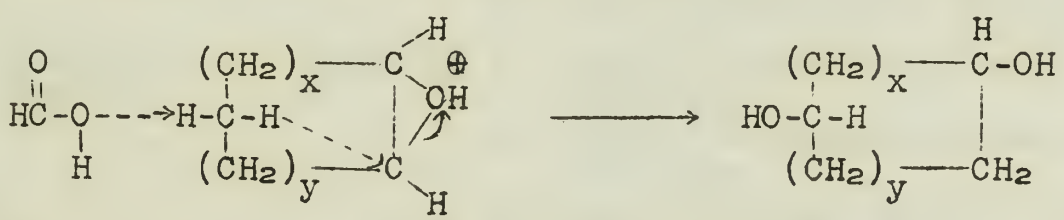


Table I provides a comparison of the products and yields in the reactions indicated.

Up to the present time no transannular products have been detected in reactions of cyclic compounds of 12 members or above (18). Until 1956 this situation existed with cyclic compounds of 7 members or less

(15,19). Then it was found that when cycloheptene oxide was heated on a steam-bath with dilute hydrochloric acid, a transannular reaction product, a diol with an empirical formula $C_7H_{14}O_2$, was formed (see Table I,C) in addition to the "normal" products (A,B) which had been found previously (20). The diol (C) was identified as cis-1,4-cycloheptanediol by comparing it with the cis-1,4-diol made by an unequivocal synthesis.

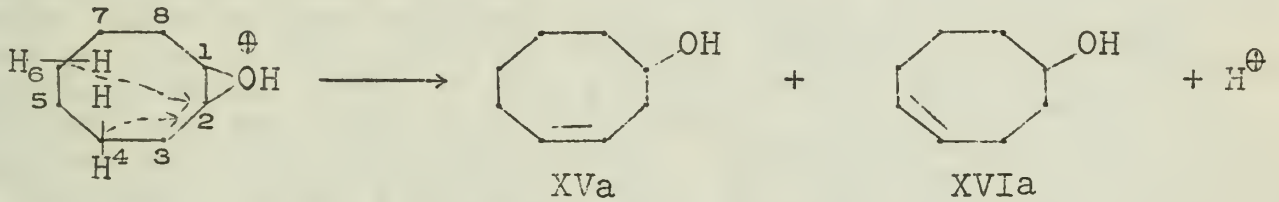
Cope found more recently that cyclohexene likewise could undergo transannular reactions (21). Cyclohexene was treated with a mixture of formic acid and hydrogen peroxide, and transannular reaction products were formed. The cyclopentanediol (C) was believed to have been formed from impurities which were found in the starting material (namely 1-methyl-cyclopentene and methylenecyclopentane). The previously postulated mechanism for this type of transannular reaction seems to break down in this case, since if a concerted, double Walden inversion took place, cis-1,4-cyclohexanediol instead of the trans isomer would have been obtained. Probably the reaction is not

TABLE I

Cycloölefin	Reactant	Products	Yield
1. cycloheptene oxide	dilute HCl	A. trans-1,2-cycloheptanediol	42%
		B. 2,2'-dihydroxydicycloheptyl ether	0.4%
		C. cis-1,4-cycloheptanediol	2%
		D. unidentified oil	1%
2. cyclohexene	HCOOH + H_2O_2	A. trans-1,2-cyclohexanediol	85%
		B. trans-1,4-cyclohexanediol	0.03%
		C. 1-methyl-trans-1,2-cyclopentanediol	0.4%
		D. 2 stereoisomeric 2,2'-dihydroxy-dicyclohexyl ethers	8%
3. cis-cycloöctene oxide	HCOOH	A. trans-1,2-cycloöctanediol	5-19%
		B. cis-1,4-cycloöctanediol	23-30%
		C. 3-cycloöcten-1-ol (XVa)	17%
		D. 4-cycloöcten-1-ol (XVIa)	13%
		E. Unidentified bicycloöctanol	0.1%
		F. Cycloöctanone	--
		G. 1,4- and 1,5-epoxycycloöctane	--
4. trans-cycloöctene oxide	HCOOH	A. trans-1,4-cycloöctanediol	33%
		B. trans-1,3-cycloöctanediol	1%
		C. 4-cycloöcten-1-ol	12%
		D. hexahydro-o-tolualdehyde	25%
		E. 1st liquid glycol, $C_8H_{16}O_2$	16%
		F. 2nd liquid glycol, $C_8H_{16}O_2$	13%
5. cycloöctene dibromide	CH_3COOAg	A. trans-1,2-cycloöctanediol diacetate	2%
		B. trans-1,4-cycloöctanediol diacetate	8%
		C. cis-1,4-cycloöctanediol diacetate	2%
		D. 3-cycloöcten-1-yl acetate)	56-58%
		E. 4-cycloöcten-1-yl acetate)	
6. cycloöctene dibromide (at least 77% trans)	$(Et)_4NOCCH_3$ (O)	A. 1-bromocycloöctene	9%
		B. 2-cycloöcten-1-yl acetate	45%
		C. cis-2-bromocycloöctyl acetate	9%
		D. trans-1,2-cycloöctanediol diacetate	5%

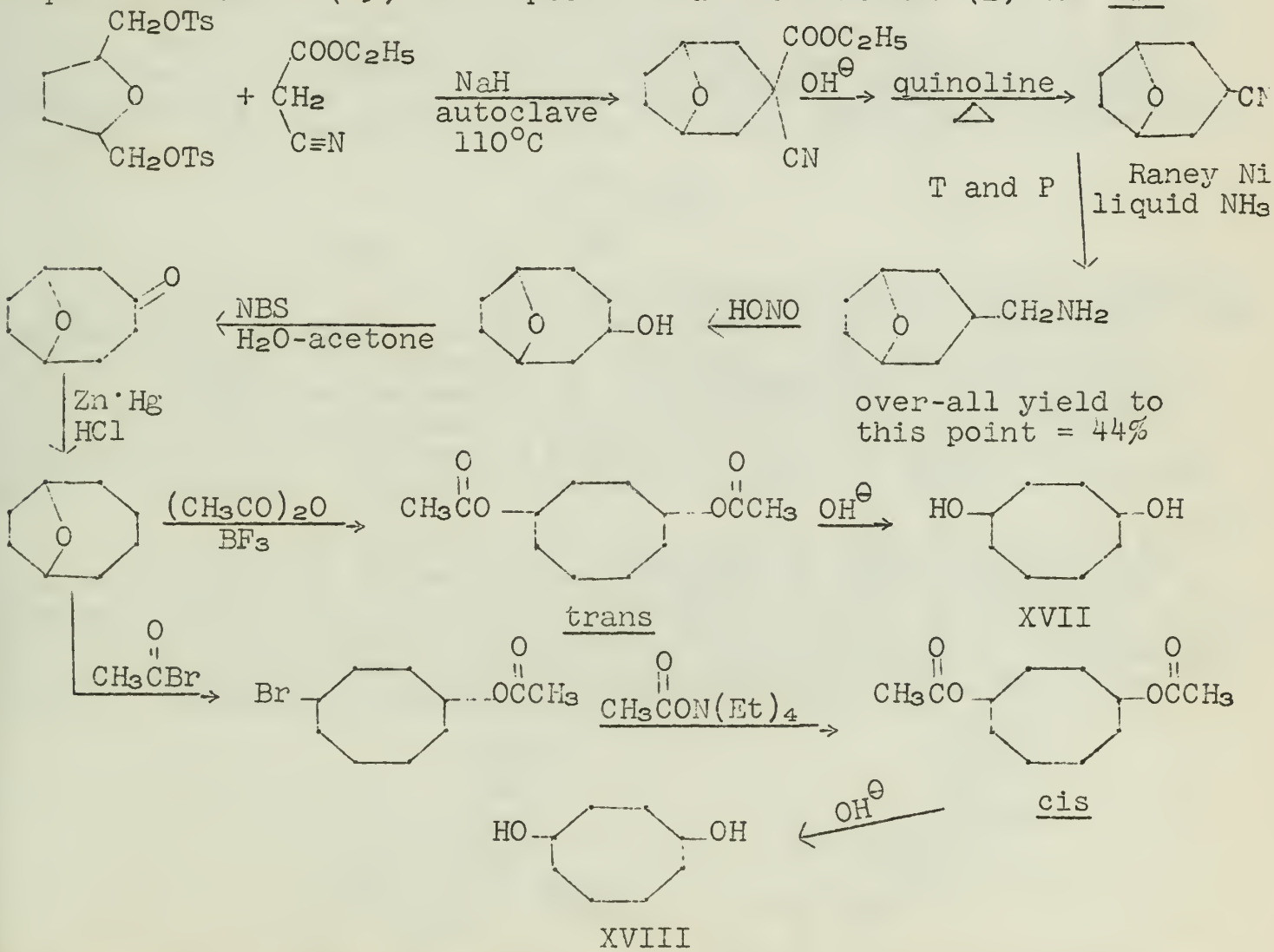
completely concerted so that a carbonium ion is in existence at C_4 long enough to allow the more stable trans-1,4-diol (equitorial hydroxyl groups) to form.

In 1952 Cope (13) investigated the solvolysis of cis-cyclooctene oxide with formic acid. Recently he has reinvestigated this reaction (22), and he has found some additional products (C-G). No 2-cyclooctene-1-ol, which would be the "normal" product, was found to be present. The unsaturated alcohols (C,D) represent products formed by transannular reaction with a 1,3- or 1,5-hydride shift and a loss of a proton from C_3, C_5, or C_7,



XVa XVIa

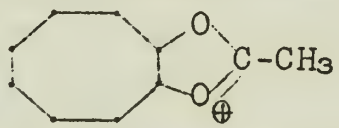
or else, (b) a dehydration of cis- 1,4-cyclooctanediol (B) which was one of the observed products. Previously the configuration of the 1,4-diol (B) had not been known, but both the trans- (XVII) and the cis-1,4-cyclooctandeiol (XVIII) have been synthesized in an unequivocal manner (23) which proved that this isomer (B) was cis.



In a similar manner the two stereoisomers of 1,5-cyclooctanediol were synthesized (24).

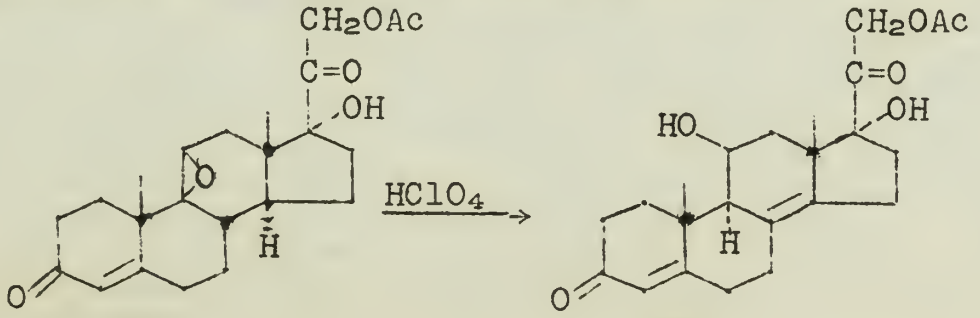
Trans-cyclooctene oxide was prepared by Cope (25) in 93% yield by treating cyclooctene with peracetic acid. Ziegler and Wilms (26) had found that a water-insoluble fraction separated from the aqueous solution when trans-cyclooctene oxide was solvolyzed with dilute sulfuric acid, but no products were isolated. Cope found that transannular products were formed when trans-cyclooctene oxide was allowed to react with formic acid. It could not be determined which isomer or whether a mixture of isomers of hexahydro-o-tolualdehyde (D) was formed because it was actually isolated as a stereoisomeric mixture of the corresponding acids. The unusual ring contraction which this product represents is probably due to the proximity of the opposite sides of the original ring, and also because of the great amount of ring strain which is probably inherent in the trans-cyclooctene oxide. Both of the glycols formed (E,F) were shown to be different from the eight possible isomeric cyclooctanediols by comparison of their infrared spectra. They both were shown not to be 1,2-glycols by the periodate test, and they each have one C-methyl group by the Kuhn-Roth determination. Undoubtedly a ring contraction is involved here also. The other three products (A,B,C) could have been formed by mechanisms which have been discussed already.

When cyclooctene dibromide (at least 77% trans) is allowed to react with silver acetate in dry acetic acid only about 2% of the "normal" product, trans-1,2-cyclooctanediol diacetate, (A) is formed (27). Winstein and Buckles (28) have shown that trans-1,2-dibromo compounds react with silver acetate by way of a cyclic acetoxonium ion (XIX). This structure is similar to the protonated epoxide which

XIX 

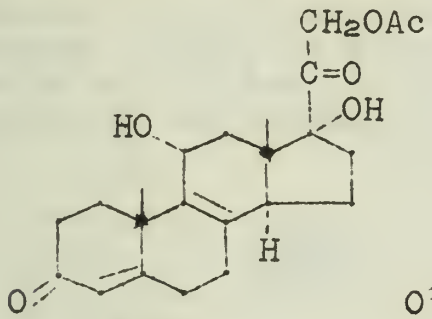
is the intermediate in the "abnormal" hydroxylation of cis-cyclooctene. Compound XIX undergoes a normal displacement reaction with acetate ion to form a trans-1,2-diacetate (A). However, one cannot say that there is a concerted mechanism in the transannular reaction since, unlike the other examples in the cyclooctene series, the reaction is not stereospecific. Rather, a mixture of cis and trans isomers (B,C) is obtained. Thus a step-wise mechanism is probably involved.

A transannular hydride shift has likewise been found with a reaction in the steroid series (29). Treatment of 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (XX) in chloroform at 0° with 60% perchloric acid resulted in the formation of cortisone acetate in a 15% yield and also a transannular reaction product, 17α-hydroxy-$\Delta^{8(14)}$-dehydrocorticosterone 21-acetate (XXI), in a 65% yield.

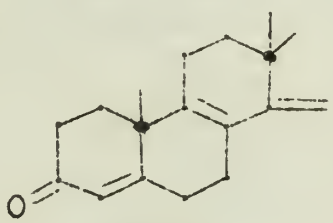


XX XXI

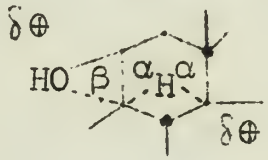
The detailed proof of structure XXI will not be given here. Treating 17 -hydroxy-$\Delta^{8(9)}$-dehydrocorticosterone 21-acetate (XXII) with 60% perchloric acid produced exclusively the heteroannular $\Delta^{8(14)}$-diene (XXIII). This rules out XXII as a possible intermediate in the conversion of XX to XXI. It was shown that XXI was not produced as a result of a 1,2-shift of the 8β-H by treating 9α,17α-dihydroxy-corticosterone 21-acetate and 9α,11α-oxido-Δ^{4}-pregnene-17α,21-diol-3,20-dione 21-acetate, respectively with 60% perchloric acid. There was no appreciable reaction. It can be seen that these systems are ideally set up as compared to XX for such a shift. Accordingly, it can be concluded that the molecule undergoes a 1,3-hydride shift (XXIV) with subsequent release of a proton from C_8.



XXII



XXIII



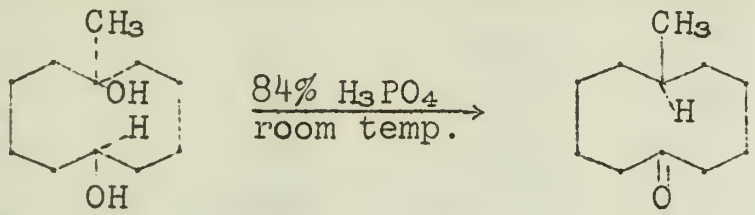
XXIV

MECHANISTIC CONSIDERATIONS OF THE TRANSANNULAR HYDRIDE SHIFT

As can be clearly seen from the reactions discussed above, most of the transannular substitution reactions appear to proceed by a concerted mechanism because of the stereospecific products produced. However, we have seen that transannular reactions do not proceed stereospecifically in every case, so it is probable that some of the reactions proceed by a step-wise mechanism.

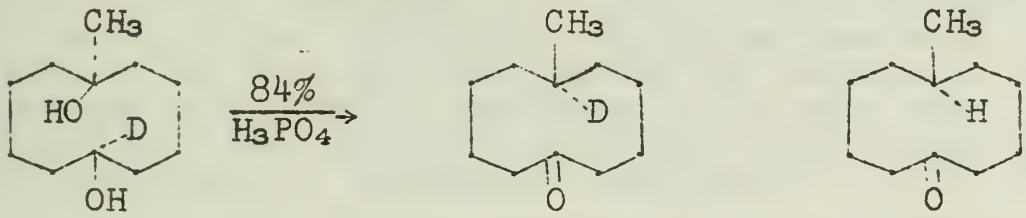
Since the reaction of cyclooctene dibromide with silver acetate in dry acetic acid described above likely proceeds by a *lim* mechanism (28), Cope (30) proceeded to investigate a similar reaction which likely involves an *N* mechanism. This was the reaction of cyclooctene dibromide with tetraethylammonium acetate in refluxing acetone. The products obtained are listed in Table I. All of the products obtained can be formed through normal displacement reactions; *i.e.*, no transannular reaction products were obtained. By contrast, when cyclooctene dibromide was treated with silver acetate, the products were predominantly the result of transannular reactions. These factors seem to indicate that the transannular hydride shift is favored by the transitory formation of a carbonium ion, such as is found in the *lim* reaction, but that it does not occur with *N* displacements. In the other reactions where "transannular" products were found, the reactions were carried out in polar media and the transition states had at least some carbonium ion character. Two other reactions, the addition of bromine to *cis*-cyclooctene forming *trans*-1,2-dibromo-cyclooctane and the reaction of hydrogen bromide with *cis*-cyclooctene oxide forming *trans*-2-bromocyclooctanol, were run in non-polar solvent (carbon tetrachloride), and only "normal" products were obtained. (It is to be noted that the intermediate in the addition of bromine to *cis*-cyclooctene is a bromonium ion, a structure similar to that of protonated *cis*-cyclooctene oxide; thus, the possibility for transannular reaction exists).

Prelog and Kung (12) noted that when 1-methyl-1,6-cyclodecanediol (XXV) was treated with 84% phosphoric acid at room temperature 6-methyl-1-cyclodecanone (XXVI) was obtained in 82% yield. A possible mechanism for this reaction is the formation of a tertiary carbonium



XXV XXVI

ion under the influence of strong acid followed by an oxidation of the secondary alcohol by means of a hydride shift. This hydride shift was shown to be a 1,6-shift rather than a 1,5-shift which would lead to the enol by the following reaction:



XXVIIa XXVII

Had a 1,5-shift taken place structure XXVIIa should have been formed. This was the first clear demonstration of a 1,6-hydride shift.

The migrating hydrogen of a transannular hydride-shift must occupy an axial position (12). This fact excludes the possibility in the above reaction of a hydride-shift by way of an ether intermediate, since in such a case the migrating hydrogen would be in an equatorial position.

The question now arises as to whether it is possible to have an alkyl radical shift, that is, a transannular pinacol rearrangement. A stereoisomeric mixture of 1,6-dimethyl-1,6-cyclodecanediols was treated with 84% phosphoric acid at room temperature. A single product (XVI, discussed previously) was obtained, but there was no sign of a 1,6-methyl transfer (12).

Prelog and his coworkers previously have shown by the use of C^{14} that when cyclodecylamine is treated with nitrous acid, 62% of the elimination product (the major product) results from classical elimination, 24% from a 1,2-hydride shift, and 14% from transannular reactions. Furthermore, 46% of the substitution product resulted from classical substitution, 33% from a 1,2-hydride shift, and 21% from transannular reactions. Recently Urech and Prelog (31) have made a similar study with the solvolysis of C^{14}-marked cyclodecyl tosylate in dry acetic acid. The reaction produces a mixture of both stereoisomers of cyclodecene, the reaction proceeding almost exclusively by elimination. The cyclodecene which was produced was oxidized to sebacic acid, the sebacic acid was subjected to successive Schmidt degradations, and the carbon dioxide which was produced in each step was collected and measured for radioactivity. In this manner the radioactivity distribution on each of the five carbon pairs ($\alpha,\beta,\gamma,\delta,\varepsilon$) could be determined. The results are listed in Table II.

TABLE II

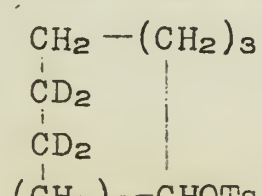
C Atoms			K	E_{cis}	E_{trans}
COOH	COOH	α	0.750	0.353	0.420
CH_2	CH_2	β	0.250	0.222	0.218
CH_2	CH_2	γ	0.000	0.129	0.096
CH_2	CH_2	δ	0.000	0.122	0.111
CH_2	CH_2	ε	0.000	0.174	0.155

K= Calculated without hydride transfer.
E_{cis} and E_{trans} = Found from cis- and trans-cyclodecene respectively.

It was found that when cis-cyclodecene was treated with anhydrous deuterated acetic acid along with sodium tosylate and sodium acetate under solvolysis conditions that there was effectively no hydrogen-deuterium exchange. Therefore, carbonium ions were not produced by the addition of hydrogen ions during the solvolysis, which would have changed the radioactivity partition if it were true. It can be concluded that the 1,5- and 1,6-hydride shifts play an important role in the solvolysis of cyclodecyl tosylate.

It was observed (31) that the extent of transannular reaction as opposed to "normal" reaction was much greater with the solvolysis of cyclodecyl tosylate than was observed with the deamination of cyclodecylamine. A possible explanation for this difference is that the deamination of cyclodecylamine requires less assistance from nearby groups such as the hydride ion than does the solvolysis of cyclodecyl tosylate. The solvolysis of cyclodecyl tosylate also probably involves an ion-pair which is more stable and longer-lived than the simple carbonium ion produced by deamination of cyclodecylamine. Hence the ion-pair from the tosylate might have a greater opportunity for a transannular reaction than would the bare carbonium ion from cyclodecylamine which might react very rapidly with the solvent.

Heck and Prelog (32) as well as Brown (33) found that solvolysis of medium ring tosylates and brosylates (especially the 8-, 9-, and 10-rings) in anhydrous acetic acid was much more rapid than the solvolysis under the same conditions of the tosylates or brosylates of any other ring size. There are two possible general explanations for this behavior (34). One is that it is due to the non-classical strain. The hydrogen atoms occupy unfavorable configurations and mutually hinder, so the formation of a carbonium ion during the course of the reaction would lead to a lessening of this strain. The second possible explanation is that the positive charge in a carbonium ion of middle ring size is not localized, but that there exists a transannularly bridged carbonium ion. If this were true, however, one would expect an isotope effect on the acetolysis rate with compound XXVIII. No isotope effect was observed.



XXVIII

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SYNTHESIS OF MACROCYCLES BY POLYMERIZATION REACTIONS

Reported by J. L. Fedrick October 28, 1957

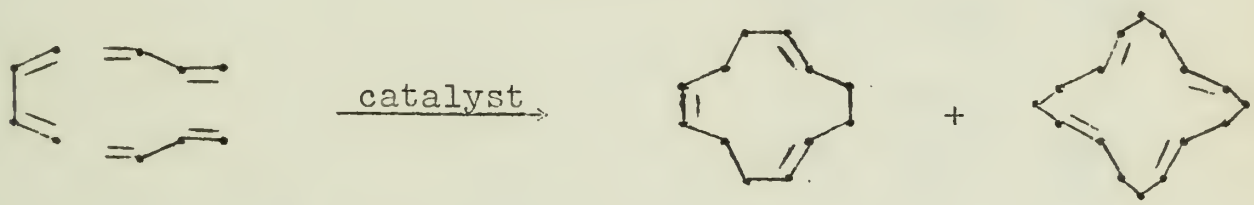
INTRODUCTION

The synthesis of large ring compounds, a challenging problem for chemists, was solved successfully thirty years ago (1). Since that time large ring carbocycles have been made by pyrolysis of heavy metal salts of aliphatic terminal dicarboxylic acids, by treatment of the corresponding dinitriles with a sodium alkylanilide, by the reaction of diketenes with tertiary amines (2), by the acyloin condensation of the diester (3) and by condensing terminal dibromoalkylbenzenes with sodium- or lithium-phenyls (4, 5). Recently new methods for the synthesis of ring compounds larger than those previously reported and for the preparation of new ring systems have been developed from polymerization studies. This seminar will be restricted to the synthesis of these homocyclic systems.

DIENE CYCLIZATION

A modification of the butadiene polymerization reaction has been found in which the reaction products are primarily macrocyclic compounds (6). Trans, trans, cis-dodecatriene(I) has been prepared in this way by trimerization of butadiene on a Ziegler type catalyst.

Figure 1



I

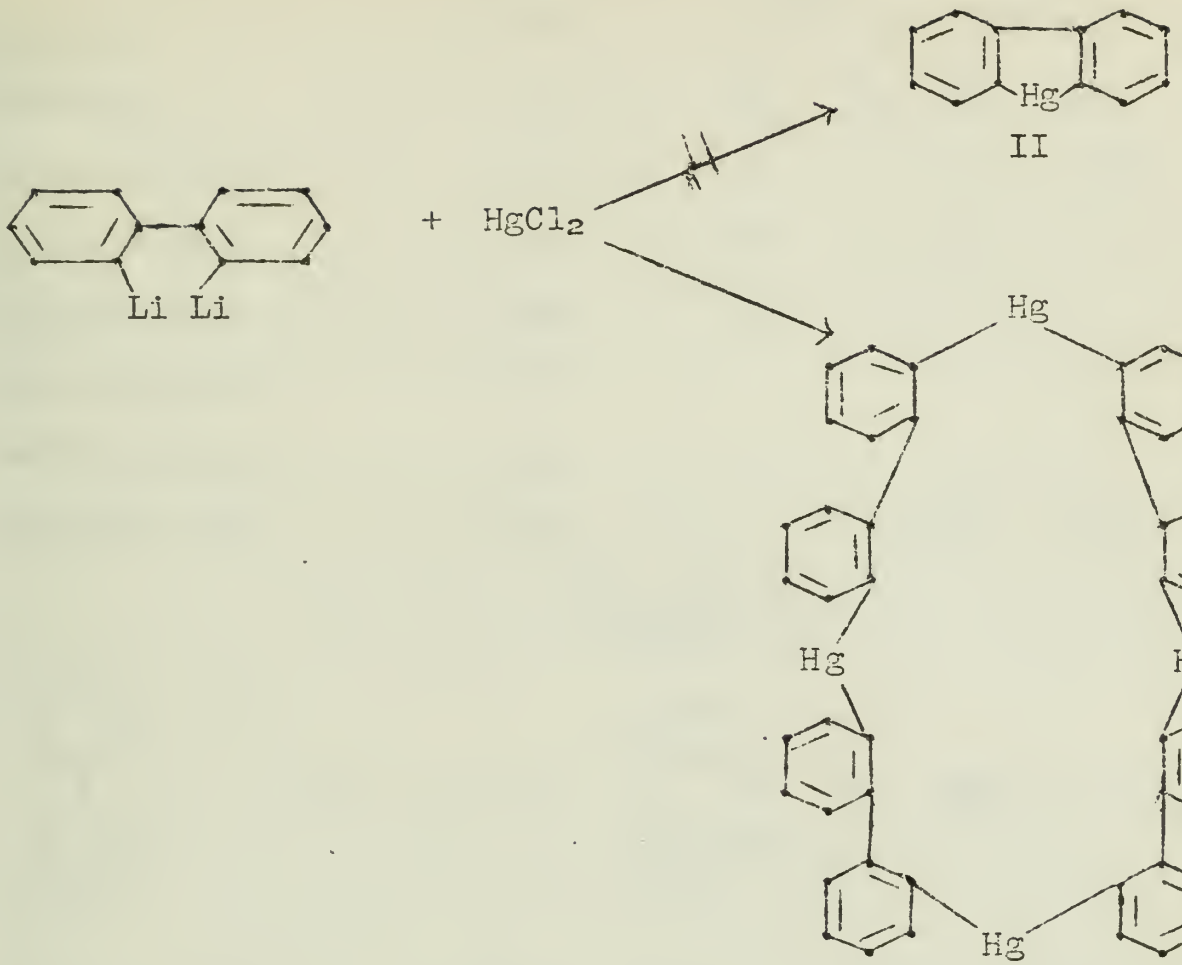
80% b.p. 100
m.p. -18°

In addition vinylcyclohexene, cis,cis-cyclooctadiene, cyclohexadecatetraene and other isomers of these polymembered cyclic compounds were isolated. If another heavy metal is used as a catalyst component, a 90% yield of mixed isomers of dodecatriene is formed, from which the all trans isomer can be isolated. The structure of cyclododecatriene was established by its infrared spectrum, hydrogenation, analysis and oxidative cleavage. The nature of the catalysts used in these reactions was not disclosed.

ORTHOPHENYLENE COUPLING

In the reaction between 2,2'-dilithium biphenyl and mercuric chloride, it would not be unreasonable to expect that a five-membered heterocyclic mercuric compound (II) would be formed (7, 8).

Figure 2



III

97% m.p. 335°

A molecular weight determination on the reaction product, however, proved it to be the heterocyclic tetramer (III); which is in agreement with the compound's high melting point. Similar results were obtained by the substitution of zinc chloride for mercuric chloride in this reaction sequence. Stable metal organic compounds such as these are formed only from such metal ions as Hg^{++} and Zn^{++} that have a closed outer electron shell. If metal ions having an open outer shell are treated with 2,2'-dilithium biphenyl at room temperature an immediate black precipitate of finely divided metal appears with coupling of the biphenyl rings. If the dilithium biphenyl is treated with ferrous chloride at -60°, cobaltous chloride at -30° or with nickel chloride at -5° no visible reaction is observed. After three days standing these reaction mixtures give negative Gilman tests, indicating that the dilithium compounds have reacted completely, possibly with the formation of structures such as III. When heated to reflux each of the above reaction mixtures formed a black precipitate. After an extended reaction period these reaction mixtures were separated by chromatography on alumina with the subsequent isolation of biphenyl (IV), ortho-quaterphenyl (V), ortho-hexaphenyl (VI), ortho-octaphenyl (VII), tetraphenylene (VIII), hexaphenylene (IX) and octaphenylene (X).

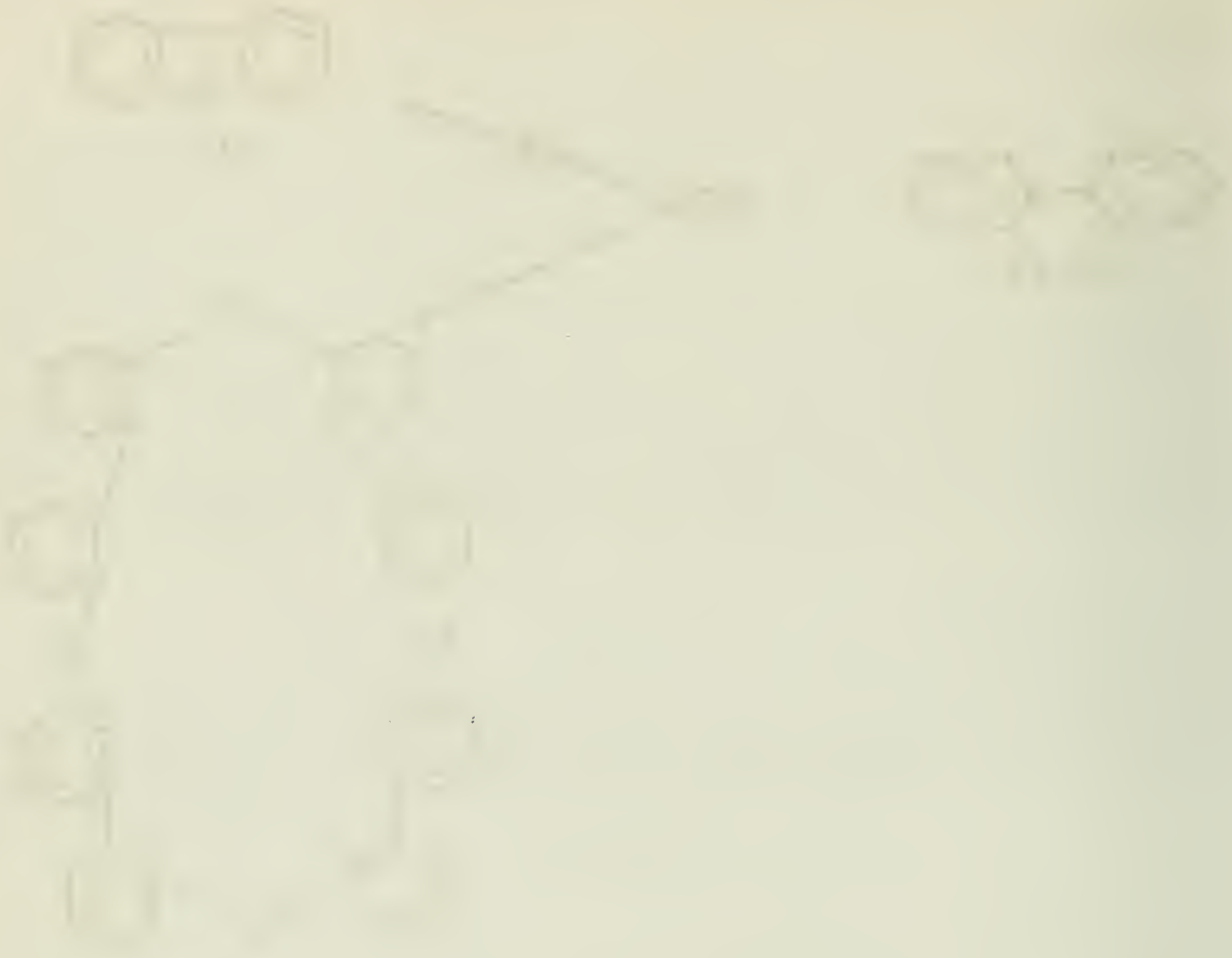
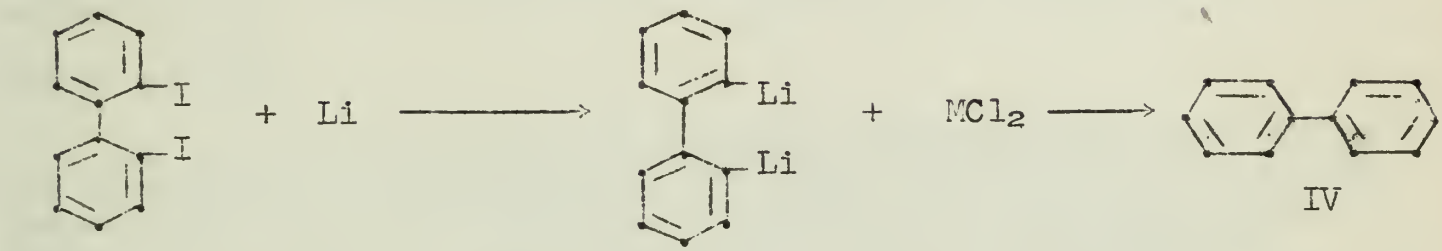


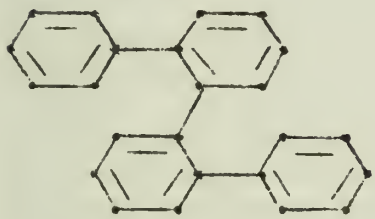
Table I

cooling	m.p.	$FeCl_2$ −	$FeCl_2$ +	$CoCl_2$ −	$CoCl_2$ +	$NiCl_2$ −	$NiCl_2$ +
diphenyl	71	34	79	20	16	22	11.5
o-quaterphenyl	119	3	1	3	0.4		
o-hexaphenyl	217	5	5	8	1		
o-octaphenyl	320	1					
tetraphenylene	233			1	3	44	46
hexaphenylene	335			1	1		
octaphenylene	429		0.3	20	17.5		

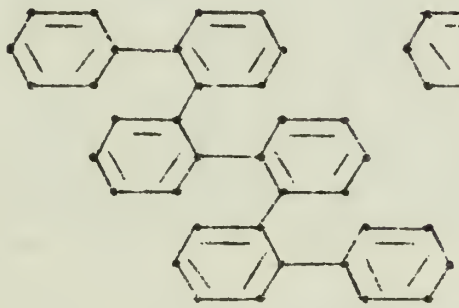
Figure 3



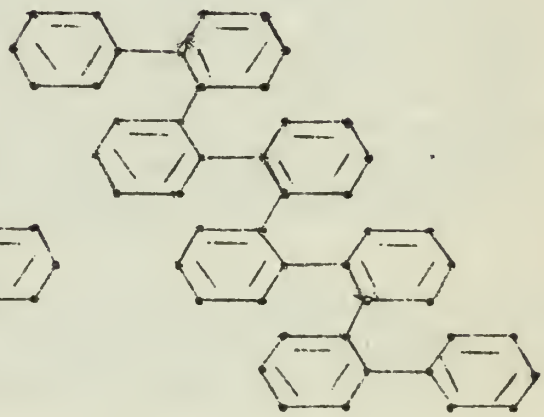
IV



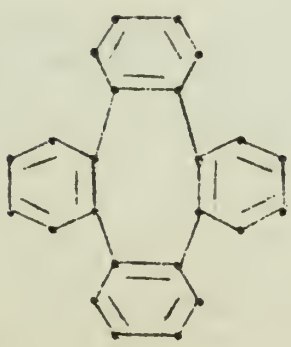
V



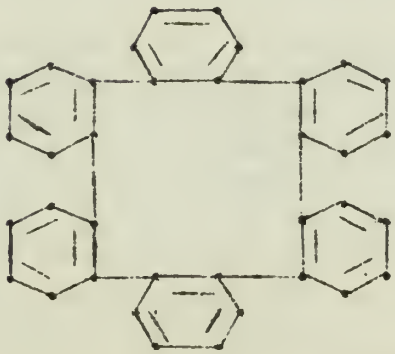
VI



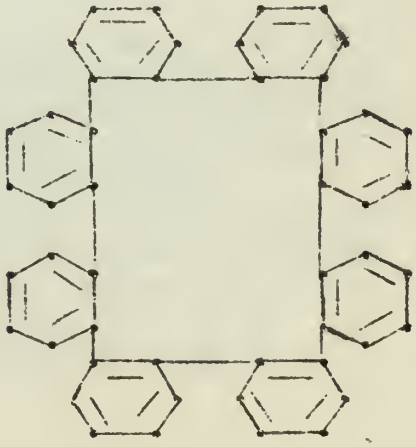
VII



VIII



IX



X

Compounds VI, VII, IX and X were previously unknown. These structures were established by means of infrared and ultraviolet absorption spectra and by determination of molecular weights. Molten pyrene was used as a solvent for IX and X. The infrared spectra of the three linear polyphenylenes exhibit monosubstitution bands which decrease in intensity with increasing molecular weight. This is consistent with the decreasing ratio of terminal monosubstituted aromatic to disubstituted aromatic groups with increasing chai length. Similarly, no monosubstituted band could be found in the infrared spectra of the three cyclic polyphenylenes. That the phenyl rings of these macrocyclic systems are not co-planar can be seen from molecular models and from the ultraviolet adsorption spectra.

A mechanism for this reaction involving diradicals is unlikely since diphenylene, an expected product from such a radical, was not isolated. Nor would it explain the great difference in the reaction of 2,2'-dilithium biphenyl with ferrous chloride, cobaltous chloride and nickel chloride. It should also be noted that the only cyclic products that were obtained in high yield were tetraphenylene and octaphenylene.

DIYNE COUPLING

The oxidative coupling of terminal acetylenes (R—C≡C—H) to the corresponding α-diacetylenes (R—C≡C—C≡C—R) is one of the few reactions in which two molecules are linked together to give a symmetrical product. The reaction has become of considerable synthetic importance, since not only acetylenic hydrocarbons (9, 10) but also acetylenic alcohols, amines, nitro compounds, carboxylic acids and esters usually give coupled products smoothly and in high yield. The reaction, which takes place under mild conditions, may be brought about by oxidizing the cuprous derivative of the acetylene with air and oxygen, cupric chloride, hydrogen peroxide, potassium ferricyanide or simply by heating or by oxidizing the acetylenic Grignard derivative with iodine or cupric halides.

In the commonly used cuprous chloride coupling reaction, cupric ion oxidizes the ethynyl group to form a dimer and an insoluble cuprous acetylide. Following this initial reaction the cupric salt

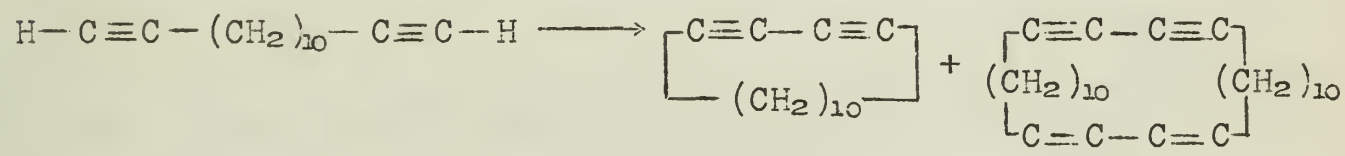
$$4\ R—C\equiv C—H\ +\ 2\ Cu^{++} \longrightarrow R\text{-}C\equiv C\text{-}C\equiv C\text{-}R\ +\ 4\ H^{+} +\ 2\ R\text{-}C\equiv C\text{-}Cu$$

is regenerated by air oxidation. It has been found that coupling of simple monoethynyl compounds can be carried out with excess cupric acetate in methanolic pyridine (11, and that under these conditions the cuprous derivative does not precipitate. If the intermediate cuprous derivative of an $\underline{\alpha},\underline{\omega}$—diyne has similar solubility properties then it might be made to cyclize to form a ring compound. Such a synthetic method would make cyclic polyacetylenes available that would be difficult to prepare by conventional routes (12, 13, 14). Tetradeca-1,13-diyne was chosen as a candidate for this oxidation, since a study of molecular models indicates that a

twelve-membered ring is the smallest stable ring that would accommodate a rigid linear six carbon conjugated diyne unit.

Reaction of tetradeca-1,13-diyne with cupric acetate in methanol and pyridine gave a reaction mixture from which 20 to 40% of cyclic diyne (XI) and 30 to 10% of cyclic tetrayne (XII) were isolated. The combined yield of these products was approximately 50% with the relative proportions of each being dependent upon experimental conditions. Cyclotetradecane-1,3-diyne (XI), a colorless viscous liquid, reddens rapidly on standing.

Figure 4



XI 20-40% m.p. 18

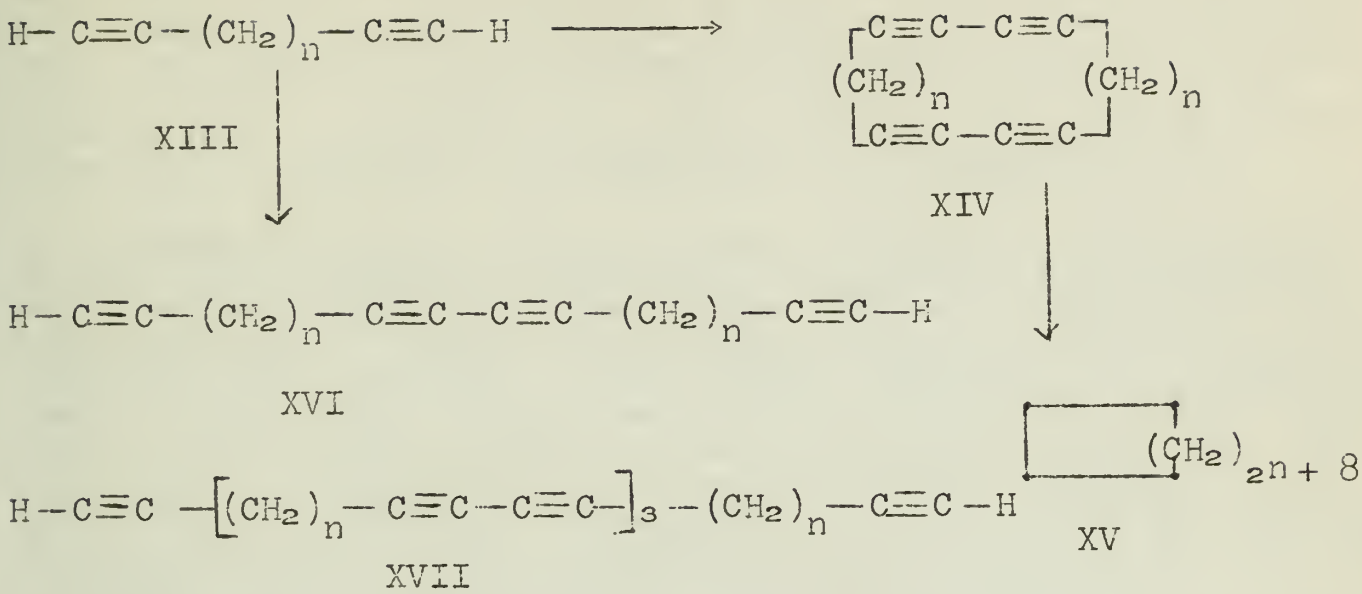
XII 30-10% m.p. 101

The tetrayne (XII) was more stable than XI but a red film slowly developed upon its crystalline surface. The structure of the cyclic monomer was established from its infrared and ultraviolet spectra and by catalytic hydrogenation to cyclotetradecane. Molecular weight and absorption spectra determinations proved the dimer to be cyclooctacosa——1,3,15,17-tetrayne. Further confirmation of the structure was obtained by its hydrogenation to the known hydrocarbon, cyclooctacosane.

Steric strain prevents simple cyclization of an α,ω-diyne such as XIII if the carbon chain has less than twelve members. Diynes such as these would be forced to form cyclic dimers instead. To test this hypothesis several diynes of the general formula, XIII, in which n was varied from two to six, were subjected to coupling (2,9,15,16). All of these reactions were carried out at 55° by bubbling oxygen through a mixture of the diacetylene, cuprous chloride and ammonium chloride in acidic aqueous ethanol. The products in each case were purified by means of chromatography on alumina. This reaction sequence is shown in figure 5 and the experimental results are recorded in table II.

The structures of the cyclic tetraynes were established by their infrared absorption spectra which have bands at 2240 $cm.^{-1}$ (disubstituted α-diacetylene) but none at 3300 $cm.^{-1}$ (H—C≡C—) or at 2100$cm.^{-1}$ (—C≡C—). Similarly the cyclic products failed to give a

Figure 5



a. n=2 d. n=5
b. n=3 e. n=6
c. n=4

Table II

n	type XIV	type XVI	type XVII
2	0% --	28% m.p. 99	20% m.p. 167
3*	12% explodes 115	26% b.p. 110/0.7 mm	18% m.p. 60
4	8% m.p. 158	45% b.p. 119/0.1 mm	19% m.p. 92
5	2% m.p. 205	58% m.p. 75	0%
6	0% --	60% m.p. 30	3% m.p. 59

* The smallest ring for which a "Catalin" model can be constructed is that in which n is three.

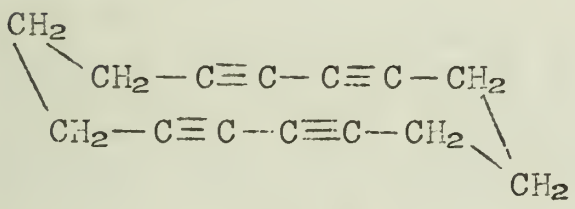
precipitate with silver nitrate as did the linear compounds XVI and XVII. That the infrared spectra offer valid structural evidence for the cyclic compounds is apparent since the spectra of the linear polyenes XVI and XVII exhibit all four of the above mentioned bands. A conclusive proof of each of these structures was obtained by hydrogenation of each acetylide to the corresponding saturated hydrocarbon.

The smallest diacetylene investigated, hexa-1,5-diyne, failed to give any cyclic product. A study of molecular models has shown that the smallest example that can be constructed for these cyclic

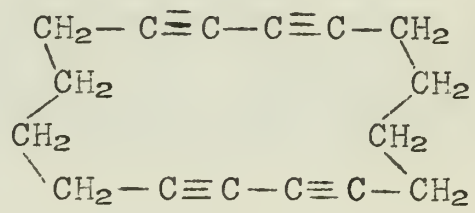
compounds is that of cyclotetradeca-1,3,8,10-tetrayne (XIV-b) (2). The cyclic dimerization of octa-1,7-diyne (7) and nona-1,8-diyne (2) went smoothly but deca-1,9-diyne failed to give any cyclic product. The formation of this cyclic system appears to proceed directly from two molecules of the monomer by coupling at both ends rather than by way of the dimer XVI. This deduction is based on the observation that repeated attempts to cyclize XVI-c failed; however, this may be a matter of insolubility of the reactants (9).

Cyclotetradeca-1,3,8,10-tetrayne (XIV-b) the smallest member of this cyclic system is represented in figure 6 and is compared with cyclooctadeca-1,3,10,12-tetrayne (XIV-c). A molecular model indicates that it forms a strainless ring and that the two α-diacetylene rods are very close to each other. Because of this closeness there is electronic interaction between the adjacent α-diyne groups. This is made evident in the compound's physical properties. That this diyne is different from its higher homolog is shown in its lower thermal stability. It explodes on being heated to 115° while the larger ring compound is stable at its melting points. Another difference between these cyclic homologs is that the cyclotetradeca-1,3,8,10-tetrayne is more polar than its straight chain analog while the reverse is true of XIV-c.

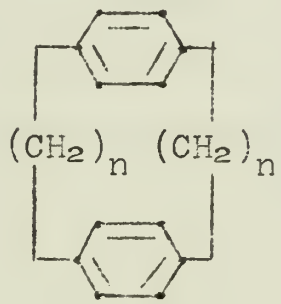
Figure 6



XIV-b



XIV-c



XVIII

The ultraviolet spectra of the cyclic tetraynes larger than cyclotetradeca-1,3,8,10-tetraynes are all similar and show maxima at 226, 239 and 253 mμ and minima at 233 and 249 mμ. A striking difference is shown by the spectrum of cyclotetradeca-1,3,8,10-tetrayne (XIV-b). The highest wave-length maximum is displaced to 263 mμ and the highest wave-length minimum to 258 mμ. Therefore, there is appreciable electronic interaction between the parallel α-diacetylene groups when they are separated by no more than three

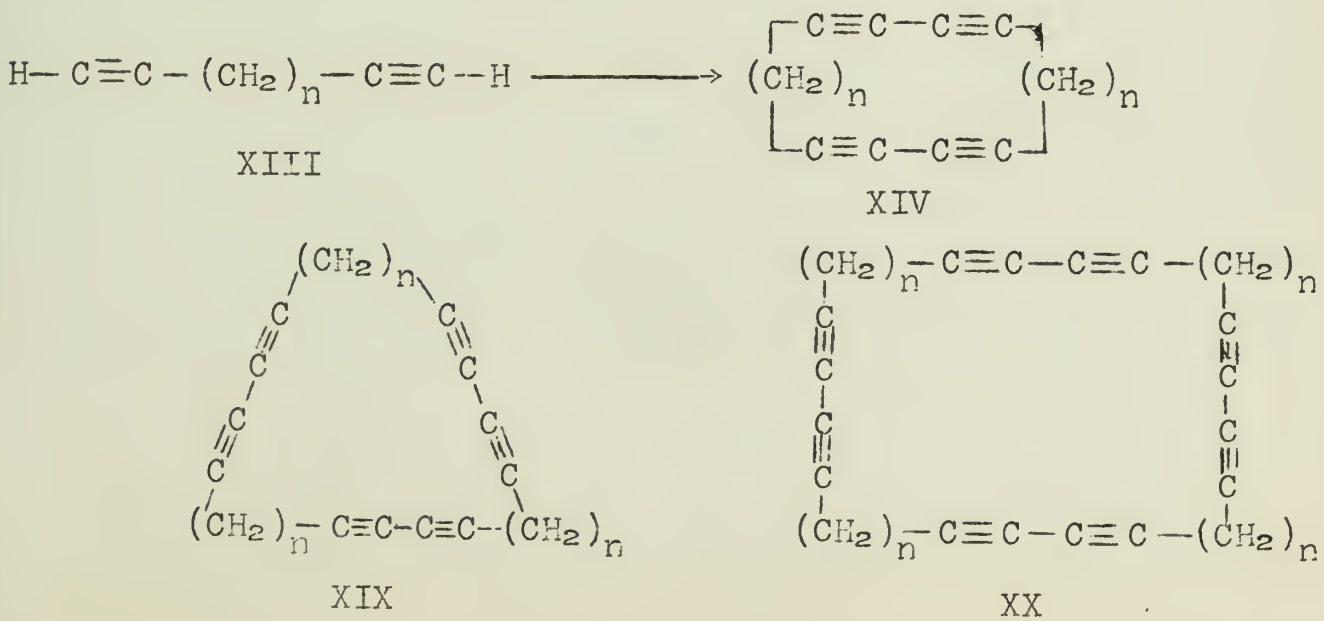
methylene groups. A similar phenomenon has been observed in the paracyclophane series (17). Symmetrical paracyclophanes (XVIII) that have aromatic functional groups separated by more than three methylene groups are normal, and those that are separated by less than three such groups have ultraviolet spectra in which the maxima are displaced to higher wave lengths.

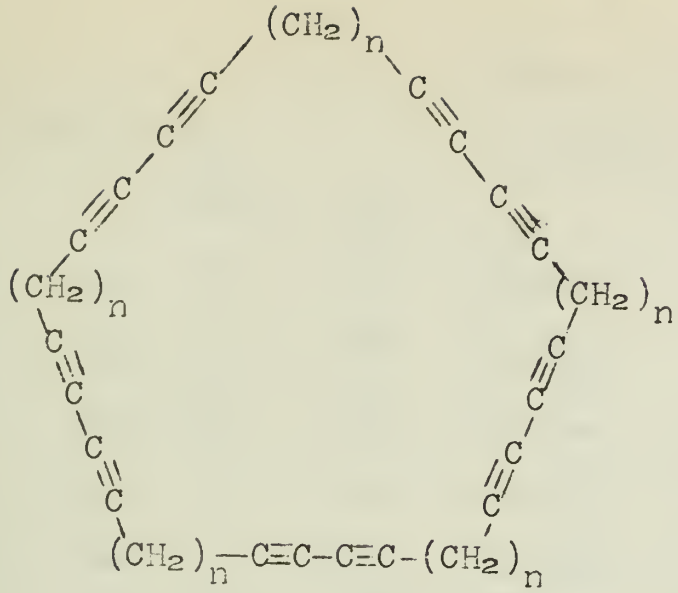
Since an α-diacetylene chain and the carbon substituents at either end ($\geq C-C\equiv C-C\equiv C-C\leq$) form a rigid straight six-carbon rod, the cyclic dimer, cyclotetradeca-1,3,8,10-tetrayne (XIV-b), can be considered as a cyclohexane in which two opposing bonds have been elongated by the insertion of α-diacetylene groupings. Like cyclohexane it can exist either in the chair or boat form. X-ray analysis of the crystalline compound has shown that the molecule has a center of symmetry and therefore exists in the chair conformation.

The oxidative coupling of α,ω-diynes containing two, three, four and five methylene units in aqueous ethanol may have stopped at the cyclic dimer stage due to insolubility of the products. Multiple coupling might occur if the reaction intermediate in the coupling step could be kept in solution. Pyridine has been found to be a better solvent for this reaction than aqueous ethanol; therefore, the coupling of the previously mentioned diynes was repeated in the presence of cupric acetate in pyridine under the conditions of high dilution, a temperature of 55° and three hours reaction time.

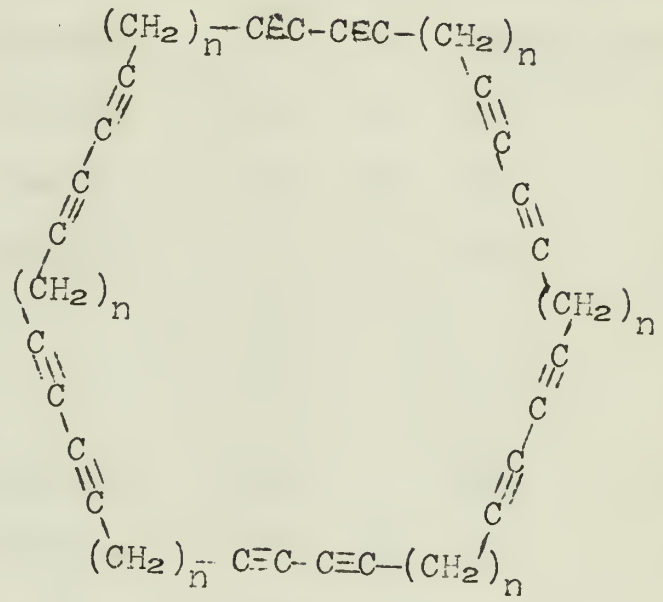
The reaction mixture in each case was separated on two hundred parts of alumina by means of elution chromatography. After the collection of three hundred to four hundred and fifty fractions the cyclic dimer (XIV), trimer (XIX), tetramer (XX), pentamer (XXI), hexamer (XXII) and higher cyclic polyacetylenes were separated in relative yields as shown in table III.

Figure 7





XXI



XXII

TABLE III

n	Cyclic Acetylide		% yield	m.p.	Hydrogenated Product	m.p.	known m.p.	mol. wt. found**	mol. wt. calculated
5	XIV	C_{18}	10	210	$C_{18}H_{36}$	71	72	mixed melting point	
	XIX	C_{27}	13	125	$C_{27}H_{54}$*	47		374	378
	XX	C_{36}	11	135	$C_{36}H_{72}$*	70		517	504
	XXI	C_{45}	4	144	$C_{45}H_{90}$*	79		618	630
	XXII	C_{54}	4	144	$C_{54}H_{108}$*	90		insoluble	
4	XIV	C_{16}	9	162	$C_{16}H_{32}$			mixed melting poin	
	XIX	C_{24}	14	173	$C_{24}H_{48}$	47	47	330	336
	XX	C_{32}	8	154	$C_{32}H_{64}$	58	59	429	448
	XXI	C_{40}	9	155	$C_{40}H_{80}$*	74		568	560
	XXII	--	--	--	--	--			
3	XIV	--	--	--	--	--			
	XIX	C_{21}	3	174	$C_{21}H_{42}$*	63		289	294
	XX	C_{28}	4	213	$C_{28}H_{56}$	47	47	389	398
	XXI	--	--	--	--	--			
	XXII	--	--	--	--	--			
2	XIV	--	--	--	--	--			
	XIX	C_{18}	6	dec.	$C_{18}H_{36}$	72		same as XIV-5	
	XX	C_{24}	6	dec.	$C_{24}H_{48}$	46		same as XIX-4	
	XXI	C_{30}	6	dec.	$C_{30}H_{60}$	57	57	416	420
	XXII	C_{42}	-	dec.	$C_{42}H_{84}$*	75		598	588

* This is a previously unknown Cycloalkane

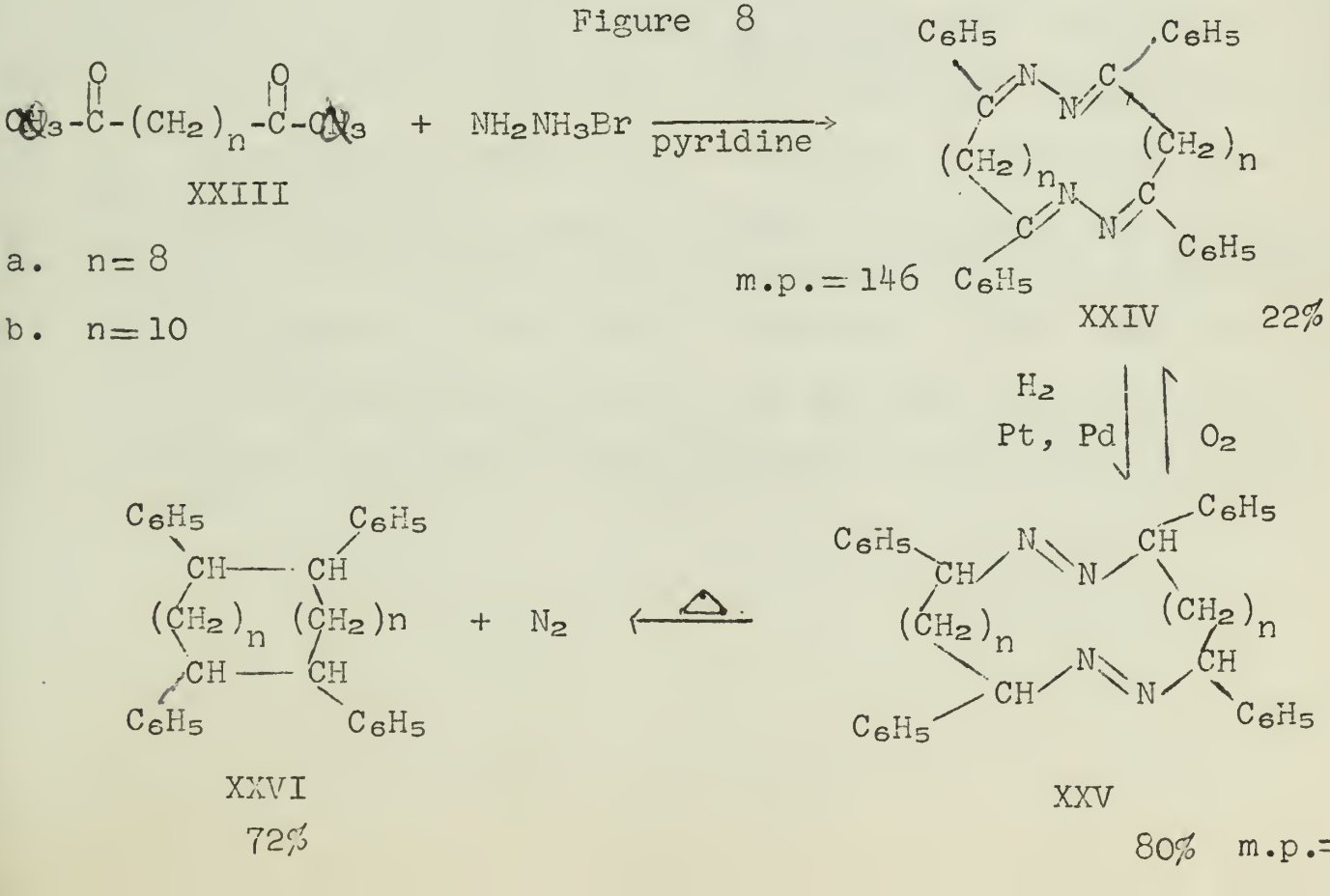
** All molecular weights were determined by the Rast Method in camphene.

All of these cyclic polyacetylenes are crystalline and were shown to be different from one another by mutual melting point depression. The absence of a band at 3300 cm.$^{-1}$ ($-C\equiv C-H$) in the infrared spectra, failure to form a precipitate with silver nitrate and the absence of a terminal methyl group (1380 cm.$^{-1}$). in the spectra of the corresponding saturated hydrocarbon indicate that the compounds are cyclic. Incorporation of hydrogen to form the known saturated hydrocarbon gave conclusive proof for many of these polyynes. Satisfactory analytical results could be obtained on the saturated cyclic compounds, but the polyacetylenes exploded on attempted combustion. Further data were gained from molecular weight determinations. This was especially important in establishing the structure of the previously unknown hydrocarbons, $C_{27}H_{54}$, $C_{36}H_{72}$, $C_{54}H_{108}$, $C_{40}H_{80}$, $C_{21}H_{42}$ and $C_{42}H_{84}$. This method of synthesis makes it possible to synthesize a number of large ring alicyclic hydrocarbons in two steps. Previously the largest alicyclic ring that had been prepared was tetratriacontane. This macrocycle is much smaller than tetrapentacontane prepared by α,ω-diyne cyclization.

AZO COUPLING

In an attempted preparation of a twelve-membered cyclic diazo compound, 1,10-diphenyl-1,10-decanedione (XXIII-a) was treated with hydrazonium bromide in dimethylformamide solution. This solution was diluted with ethanol and was added to a refluxing solution of ethanol and pyridine under conditions of high dilution (19, 20). The product that was isolated was not the twelve-membered cyclic monomer, however, but the bis azine cyclic dimer (XXIV-a). Its structure was established by determination of molecular weight,

Figure 8



analysis, quantitative hydrogenation and by comparison of the infrared and ultraviolet spectra with those of a model compound, propiophenone azine. The bis azo hydrogenation product (XXV-a) was decomposed in refluxing xylene to produce a twenty-membered cyclic hydrocarbon, 1,2,11,13-tetraphenylcycloeicosane (XXVI) in high yield The infrared spectrum and a molecular weight determination are consistent with this product. The twenty four-membered cyclic analog was made from 1,12-diphenyl-1,12-dodecanedione by the same reaction sequence and the structure was established in a similar manner.

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MECHANISM OF OLEFIN HYDRATION

Reported by N. L. Bauld November 4, 1957

INTRODUCTION

Electrophilic attack on olefinic linkages has, of course, long been recognized and subjected to quite thorough scrutiny. In particular, the addition of halogens and halogen acids to such linkages has been fairly exhaustively studied. In the case of bromination, from these studies has emerged the generally accepted formulation involving the cyclic intermediate (I), which quickly reacts with a bromine molecule or other nucleophile(1). This mechanism is implied to operate in halogen additions in general and is consistent with the pertinent facts, namely, nonconcerted, cationic, trans addition.

I

II

Halogen acid addition is known to possess characteristics identical with those listed above, but has been much less widely regarded as involving the cyclic species (II) analagous to (I). However, Hammond (2) has recently invoked this bridged ion to rationalize the trans hydrobromination observed in 1,2-dimethyl-1-cyclohexene.

In view of these considerations one could reasonably be expected to examine carefully the possibility of such a reactive intermediate in the closely related hydration reaction.

It is interesting that nucleophilic hydration of olefins can be effected when the olefinic linkage comprises part of an α,β-unsaturated carbonyl compound, e.g., acrolein or acrylic acid(3,4). However, this type of hydration occurs only with considerable urging (extended reaction times at 100° C), and will not be considered in this seminar.

GENERAL

Lucas and Everz (5) have investigated the reaction of dilute, aqueous HNO_3 with isobutene at 25° C and have established the reaction as being first order in olefin and acid at constant ionic strength and have found the reaction rate to be enhanced by an increase in the ionic strength of the medium.

Lucas and Liu (6) extended the investigation to trimethylethylene and measured the rates of hydration of this compound in various acidic media, including sulfuric, nitric, perchloric, hydrochloric, hydrobromic, p-toluenesulfonic, picric, oxalic, acetic, and dithionic acids. It was pertinently discovered in a later investigation by Ciapetta and Kilpatrick (7) that the above olefin is hydrated at essentially the same rate in the acids perchloric, hydrochloric, p-toluenesulfonic, and nitric, when the rate constants were extrapolated to infinite dilution to obliterate salt effects of the nonidentical anions. As a result, it may be safely concluded that the anions of the above acids are not significantly involved in the transition state of olefin hydration, else an anion specificity would most certainly manifest itself.

Subjected to the mentioned reaction conditions n-butenes are, incidentally, not detectably hydrated after several days.

Taft has more recently studied the reaction with an eye to its intimate mechanistics and it is largely with his work that this seminar will be concerned. Typical values of the heats and entropies of activation for the hydration reaction, obtained by Taft, are tabulated below (these values are for the hydration of dissolved olefins)(8).

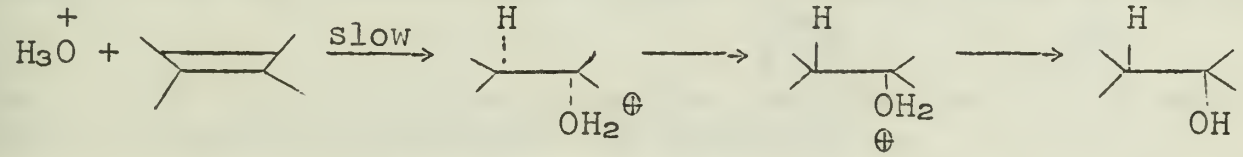
OLEFIN	TEMP. INTERVAL	$\triangle H^{\ddagger}$	$\triangle S^{\ddagger}$	ACID CONC.
Isobutene	25-50°	21.1	-7.7	.0909 M
2-methyl-2-butene	"	22.2	-5.1	.1

RATE DEPENCENCE ON ACIDITY

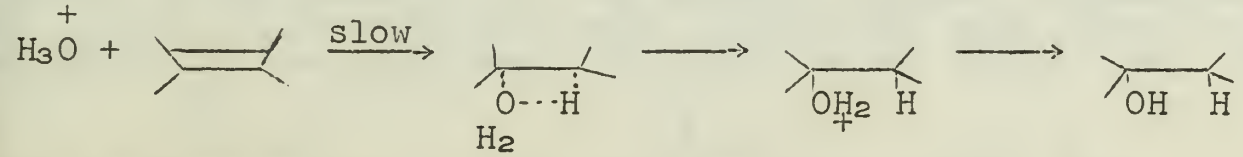
In order to divine the reaction mechanism it is necessary to establish whether the addition occurs in a concerted fashion, in a two step process, or by a more complex sequence. This is, of course, a rather delicate decision, especially since "one-step" and "two-step" are merely limiting potential reaction coördinates which grade imperceptibly into each other. However, a qualitative choice is considered possible and expedient, and to this end Taft (9,10) invoked the Hammett-Zucker criterion (11,12). According to this principle, quite empirically developed, for a reaction whose transition state differs from the reactant by only a proton, log k, the logarithm of the rate constant, will be a linear function of unit slope of the Hammett acidity function, H_o, at higher acidities, and, conversely, if the transition state differs from the reactant by more than a proton the mentioned parallelism with H_o will not be observed. Since the premises and numerous examples of the application of this hypothesis were the subject of a recent seminar (12), its validity will be tacitly assumed with no further comment.

Taft has applied this criterion to the hydration of isobutene (9) and later to 2-methyl-2-butene, methylenecyclobutane, and triptene (10). In all instances he obtained a linear plot vs. H_o. Slopes ranged from .98 to 1.11 for the various olefins. The conclusion is that the transition state is a protonated olefin, and does not contain a water molecule.

This result enables one to discount several possible mechanisms. First of all, the "concerted" mechanism (Scheme I) is precluded

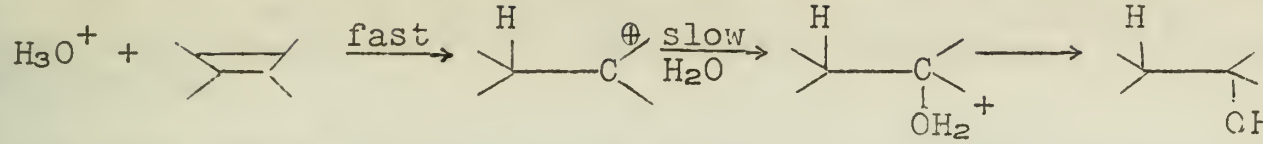


since the transition state contains a molecule of water. This includes the four center reaction (Scheme II). Secondly, the sequence



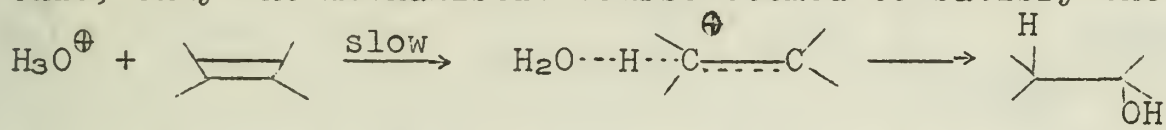
which involves a fast reaction to give carbonium ion followed by a rate determining reaction of the latter with water (Scheme III) is

impossible. At this point Taft concluded that a rate determining



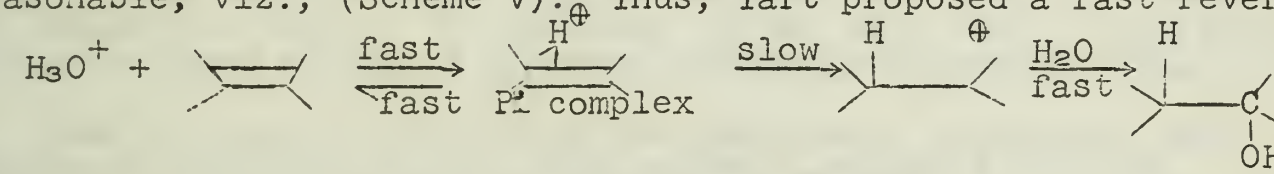
Scheme III

attack of H_3O^+ was likewise excluded on the grounds that it involved a molecule of water in the transition state. (Scheme IV) As a result of this, only one mechanistic course seemed to satisfy the kinetic



Scheme IV

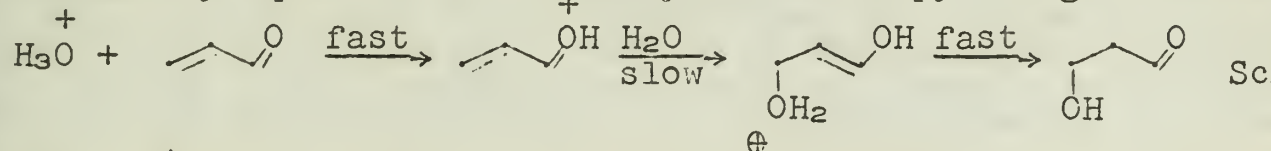
data, and, by analogy to the proposed intermediates in bromination and other electrophilic attacks on olefin linkages, this seemed wholly reasonable; viz., (Scheme V). Thus, Taft proposed a fast reversible



Scheme V

reaction to give the bridged species in V, which rearranges to the classical carbonium ion in the rate determining step (and thus no water is included in the transition state), which, in turn, reacts speedily with a molecule of H_2O. The proposed intermediate is denoted a pi complex by Taft and represented according to Dewar's notation (13). In support of his mechanism Taft expounded the following entropy data (Chart I)(10). According to this scheme the entropy of activation for the hydration of olefins should be quite small compared to that of a facsimile in which water is indeed being bonded, and which, of course, entails the loss of considerable entropy in the form of translational and rotational motions of the water molecule and its solvent shell. Indeed, $\triangle S^{\ddagger}$ is near zero for simple olefin hydration. By contrast, the hydration of α,β-unsaturated aldehydes, which is thought to pursue the mechanism (Scheme VI), and which fails to obey the H_o relationship, also in contrast to simple olefin hydration, but in good accord with the Hammett-Zucker criterion, exhibits $\triangle S^{\ddagger}$ values of about -23 cal/deg., approximately equal to the thermodynamic entropy change for the reaction.

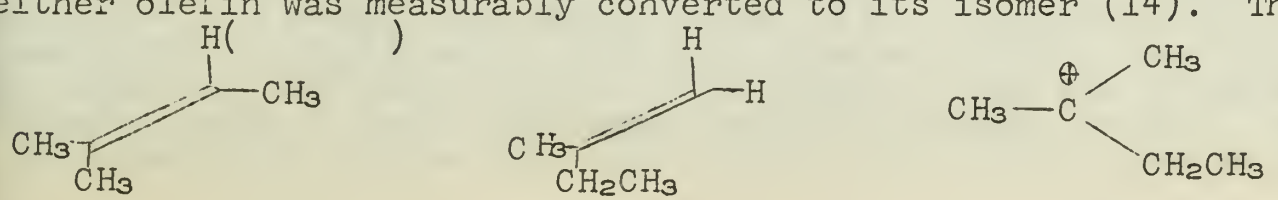
	$\triangle S^{\ddagger}$ Hydration	$\triangle S^{\ddagger}$ Dehydration
Isobutene	-3	+19
2-Methyl-2-butene	0	+15
Methylenecyclobutane	+1	---
α,β-unsaturated aldehydes		
Crotonaldehyde	-23	-2
β,β-dimethylacrolein	-23	-9



Scheme VI

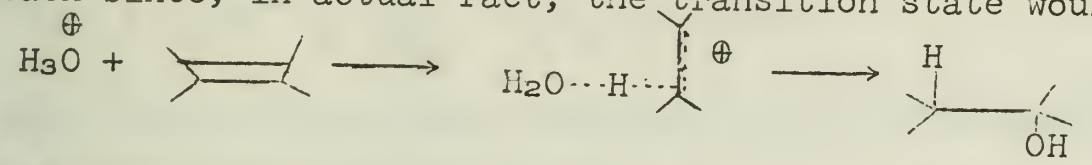
Also, $\triangle S^{\ddagger}$ for the reverse reaction, dehydration, which emancipates water, is large and positive, as expected.

In further support of this scheme it was discovered that after 50% reaction in the hydration of two isomeric olefins, trimethylethylene and asym-methylethlethylene, which produce the same carbonium ion, neither olefin was measurably converted to its isomer (14). This



precludes, again, a rate determining reaction of carbonium ion with water since in such an instance the olefin would equilibrate. These olefins equilibrate at 50° to 89% trimethylethylene and 11% methylethylethylene.

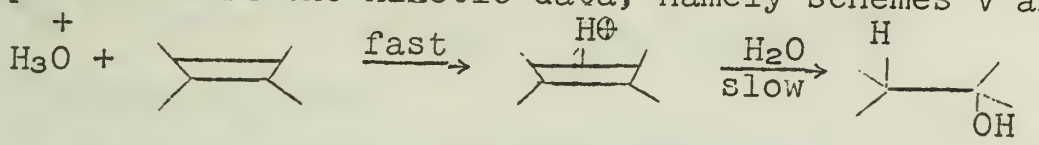
At this point Taft concluded, apparently, that his acidity function data were not inconsistent with the rate-determining hydronium ion attack since, in actual fact, the transition state would most probably



Scheme VII

not involve strong covalent bonding to a water molecule, as depicted in Scheme VII. Obviously, the other conclusions are unaffected since in all these cases a considerable covalent bond cannot be denied in the transition state. In addition, we may note that a rate determining attack of water on the pi complex intermediate (Scheme VIII) is denied.

One is thus left with only two reasonable mechanisms which are compatible with the kinetic data, namely schemes V and VII.



Scheme VIII

DEUTERIUM ISOTOPE EFFECT

The final, and probably unnecessary, annihilation of the possibility of a rate-determining carbonium ion reaction with water was performed by hydrating 2-methyl-2-butene with 1M HNO_3 in 50% deuterated water. No deuterium was discovered in the unreacted olefin after 50% reaction. The elimination of H from this carbonium ion is favored by a statistical factor of 7 and a kinetic factor of about 2 over D. The results are consistent with Taft's representation, since it requires equilibrium between olefin and pi complex, not olefin and carbonium ion, and in the former case the same ion (H^+ or D^+) which adds to the olefin is expelled in the fast reverse process.

The main purpose of the isotope effect investigation was to attempt to distinguish between the two as yet undiscredited mechanisms. In general, a rate-determining proton transfer (Scheme VII) is retarded by replacing H by D, since a deuterium bond is harder to break than a H bond. In this case it was thought that the rate would diminish linearly with increasing mole fraction of deuterium in the medium, since the only cogent example known which was thought to involve a rate-determining proton transfer, viz., the mutarotation of glucose, did so.

On the other hand, if the reaction involved a pre-equilibrium of olefin with pi complex (Scheme V), the rate would be faster in deuterium oxide than in light water, probably by a factor of about two, judging by previous examples. This effect is due to the lower basicity of D_2O than H_2O and the consequent greater acidity of D_3O^+. In this manner the prevailing concentration of pi complex will be greater in heavy than in light water, and since the rate of the reaction by this scheme is the concentration of pi complex times its specific rate of decomposition, a rate enhancement will be observed in D_2O. However it was considered that an even more crucial test was for Scheme VII

involving the pre-equilibrium, the rate in various percentages of D_2O would follow the Butler equation (15). This equation has been derived for a mechanistic sequence exactly of the type Taft has proposed as the course of olefin hydration, namely, Scheme V. The Butler equation is simply derived as follows from transition state theory.

$$S + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} SH^+ \xrightarrow{\text{slow}} \text{products}$$

$$k_H = r_H K_H K_H^{\ddagger} (a_{H^+})_H \frac{\gamma_S}{\gamma_{\ddagger}} = r_H K_H' (a_{H^+})_H \gamma_S / \gamma^{\ddagger}$$

$K_H^{\ddagger}$ = pseudo equilibrium constant for $SH^+ \rightleftharpoons$ transition state

$(a_{H^+})_H$ = activity of proton in water

K_H = equilibrium const. for proton transfer step

γ_H = rate of decomposition of transition state to give products

The similar equation for reaction in D_2O is:

$$k_D = r_D K_D K_D^{\ddagger} (a_{D+})_D \gamma_S / \gamma^{\ddagger} = r_D K_D' (a_{D+})_D \gamma_S / \gamma^{\ddagger}$$

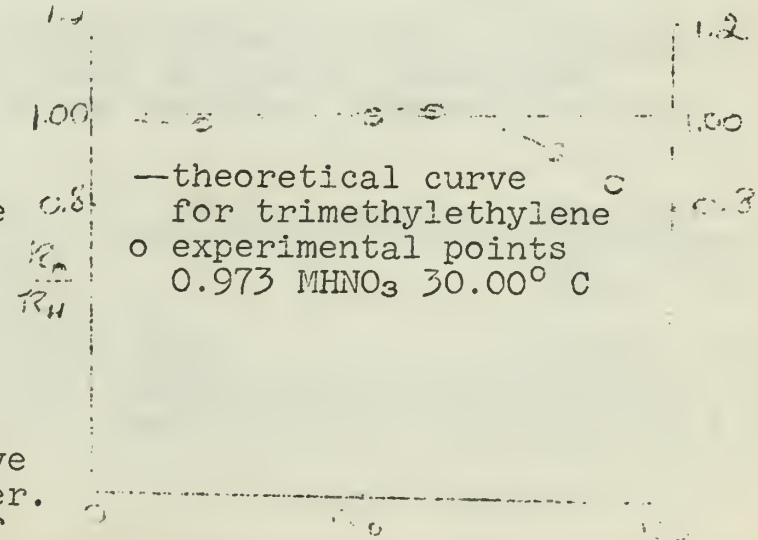
For H_2O-D_2O mixtures:

$$k_n = r_H K_H K_H^{\ddagger} (a_{H^+})_n \frac{\gamma_S}{\gamma^{\ddagger}} + r_D K_D K_D^{\ddagger} (a_{D^+})_n \frac{\gamma_S}{\gamma^{\ddagger}}$$

Where n= nole fraction deuterium in solvent. Thus we have for the ratio of rates in solvent of mole fraction n in deuterium to solvent water:

$$\frac{k_n}{k_H} = \frac{(a_{H+})_n}{(a_{H^+})_H} + k_D/k_H \frac{(a_{D+})_n}{(a_{D+})_D}$$

From the experimental k_D/k_H ratio and the activity functions for protons and deuterons in the various solvent mixtures a k_n/K_H ratio can be calculated for the mixtures. In this manner Taft calculated a theoretical curve for the hydration of 1-methyl-1 cyclopentene and trimethylethylene. As shown below the experimental data agree quite well with the theory.



This has been assumed to be convincing support of Scheme V, especially in view of the fact that the rates of hydrolysis of acetal, ethyl orthoformate and methyl acetate, which also are considered to involve a pre-equilibrium, obey the Butler equation. A sole example, the mutarotation of glucose, fails to correlate with the above equation and is thought to involve a rate-determining proton transfer. Convincingly enough, the rates of reactions which obey the Butler relation are subject to enhanced rates in deuterium oxide, and the mutarotation of glucose is retarded.

That the observed isotope effects were k_D/k_H = .82 and 1.08 for trimethylethylene and 1-methyl-1-cyclopentene, respectively, is of no significance, since, although according to Taft's scheme the prevailing concentration of pi complex in deuterium oxide is favored, the rate-determining step could have an isotope effect of its own, which very possibly would be in the opposite direction, and the magnitude of the effects cannot be assessed.

Apparently, however, it was not observed that the Butler equation can be derived in identical form for a Scheme VII reaction, involving a rate-determining proton transfer, from transition state theory. For instance k_H calculated in this way is:

$$k_H = K_H r_H (a_{H^+})_H \gamma_s / \gamma_{\neq} \qquad \text{Since } (a_{H_2O})_H = 1$$

for pure water. Comparing this with the analagous equation in the previous derivation it is obvious they are identical. In fact, the two mechanisms are indistinguishable by the transition state theory. Manifestly, the remaining part of the derivation will coincide with the previous one.

It is relevant that k_D/k_H is greater than one in one case and less than one in the other, in Taft's work. It was noted previously that for a rate-determining proton transfer deuterium is generally expected to retard the reaction. The approximately, but slightly greater than, one ratio found in one instance is easily rationalized on the basis of a stronger bond in the transition state than in the initial, weakly bonded deuteronium or hydronium species. A deuterium retardation has come to be expected only because in the glucose case another, weaker, oxonium ion is being formed, in which case the transition state must certainly maintain a weaker bond than the initial one.

In view of these considerations, the isotope effect experiments must be regarded as inconclusive with regard to discrediting one or the other of the possible mechanisms.

HYDRATION OF SMALL RING OLEFINS

Taft (16) has studied the rates of hydration and de-hydration of a series of small ring olefins in order to obtain information concerning the transition state in the reaction. The data he has compiled are listed below.

Hydration of olefins			De-hydration of carbinols		
	$K/_{KO}$	$k/_{ko}$		$K/_{KO}$	$k/_{ko}$
Isobutene	(1.00)	(1.00)			
1-methyl-1-cyclopentene	0.0073	2.29	t-BuOH	(1.00)	(1.00)
methylene cyclobutane	>200	0.60	1-Methyl-1-cyclopentanol	140	315
1-methyl-1-cyclobutene	>30	0.2	1-Methyl-1-cyclobutanol	<0.05	<.003

K = equilibrium constant k = rate constant

As expected from Brown's I-strain hypothesis, the formation of carbinol is substantially favored over olefin in the 4-membered ring compounds, as seen by the relative equilibrium constants, with isobutene as a base, while the reverse holds for 1-methyl-1-cyclopentene. Concomitant with hydration a large amount of angle strain is released in the former case, while in the latter the smaller amount of angle strain relief is overcompensated for by the increased eclipsing of CH bonds.

Interestingly, the rate of hydration exhibits no analagous contingency on structure, with a maximum variation in rate of one order of magnitude, and this is in the reverse direction as might be expected for a transition state which resembled carbinol. Here, again, it was concluded that there is no appreciable covalent bonding to water in the transition state.

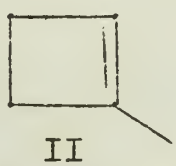
On the other hand, the formation of both transition state and olefin in the dehydration are similarly affected, indicating, of course, that the transition state partakes substantially of olefinic character.

Taft asserts that the transition state must not possess the nuclear arrangement of a classical carbonium ion, in the hydration reaction, else the rates of hydration would parallel the appropriate equilibrium. It is known that the transition state, however, is stabilized by those structural features which stabilize carbonium ions, viz., inductive and hyperconjugative electron release. The transition state, it is maintained, must then possess carbonium ion character with respect to electronic but not to nuclear arrangement, which describes accurately the proposed intermediate pi complex.

The objections to this argument are twofold. Firstly, the description applies to a transition state, and the more sluggish nuclear than electronic rearrangement could occur from either pi complex or olefin. Secondly, the observed rate sequence can be explained adequately without resorting to any such tenuous assumption.

What has to be rationalized is exactly why (I) should be hydrated faster than (II), when carbinol formation is grossly more favored in (II). The justification for such an order is easily seen if one

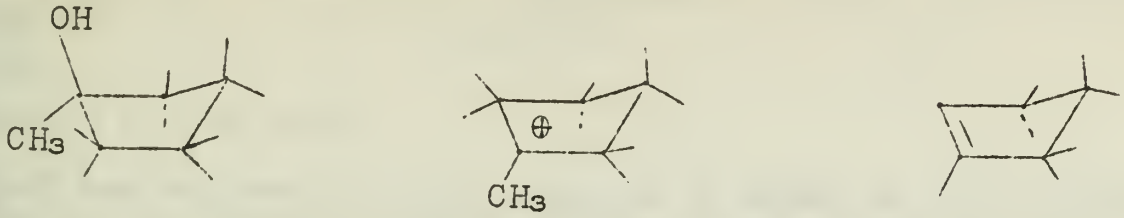
I



II

considers the relative number of bond oppositions provoked by the olefins in the equilibrium and rate processes. Thus 1-methyl-1-cyclopentene is hydrated to a much smaller extent than isobutene (less than 1/150 as much) due mainly to the two extra opposed bonds in the carbinol. Of course this factor is operative in the 4-membered analogue, also, but the angle strain relief overshelms the repulsion effects. Why, then, does not the same order of reactivity prevail in the kinetically controlled as in the thermodynamically controlled process? Firstly, we expect the quantity and relative blend of the two discussed effects in the rate process to differ from that in the equilibrium. Further,

though, we can make more definitive predictions than this. This is best done by considering 1-methyl-1-cyclopentene, 2-methylcyclopentyl carbonium ion, and 1-methyl-1-cyclopentanol.



Since the cyclopentane ring is probably in the non-planar, semichair form, upon saturating fully the cyclopentene ring two bond oppositions of the 1,2 variety are, as a first approximation, incurred. It will be seen, quite interestingly, that no bond oppositions appear upon converting the olefin to a carbonium ion. Thus, the factor which disfavored the equilibrium does not appreciably affect the rate. In fact, since at least a small amount of angle strain relief must obtain in the transition state, this olefin might be expected to hydrate faster than isobutene. This is, indeed, the case. Finally, it is obvious that in the 4-membered analogue the same factors are operative in both processes, although, of course, to a lesser degree in the rate controlled one, so that we may quite logically understand the observed rate sequence of Taft.

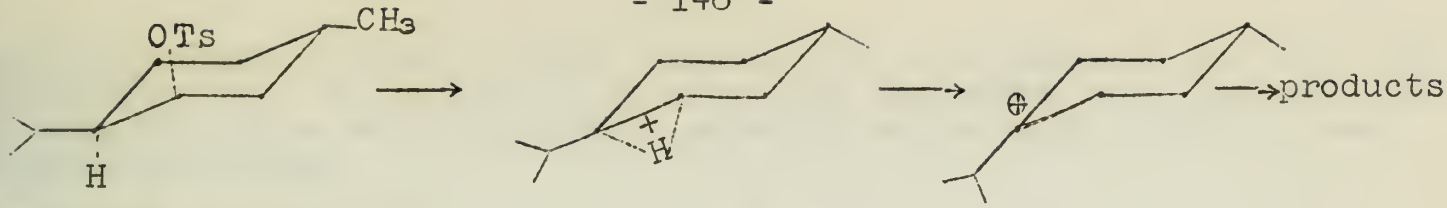
PI COMPLEX VS. BRIDGED PROTONIUM ION

The hydrogen-bridged entity which avails in those Wagner-Meerwein rearrangements which involve hydride shift would seem to represent an obvious opportunity for studying the so-called "pi complex" intermediate proposed by Taft in his olefin hydration studies. The two have been quite logically assumed to be identical by most workers.

Winstein (17) has objected to this very convincingly, using data collected from the solvolysis of 4-t-butylcyclohexyltosylates. More specifically, he has shown that, in the formolysis of the trans modification (equatorial tosylate) of the above compound 76% of olefin and only 3% rearranged alcohol were obtained, while the axial tosylate yielded 84% olefin and 32% rearrangement. According to the reverse of Taft's mechanism, elimination from a carbonium ion would involve an intermediate pi complex. Obviously if elimination involved a hydrogen-bridged species which also gave rise to rearranged product, the amount of rearrangment with the equatorial tosylate should rival that with the axial one.

Also, since Taft's scheme requires that the rearrangement to classical carbonium ion by the bridged complex is much slower than proton loss to give back olefin (this is implicit in the stipulation that the former rearrangement is the rate-determining step), if Wagner-Meerwein rearrangements involved this species little or no rearranged product would ever be isolated, elimination to olefin predominating. This clearly cannot be general.

In the formolysis of optically active neomenthyl tosylate the hydrogen shift is complete to the symmetrical species shown before any



elimination occurs (17).

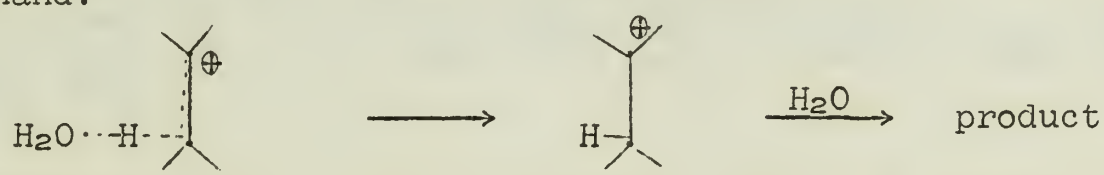
Taft has removed the last element of doubt in this issue by studying the reaction of isobutylamine with nitrous acid in D_2O. In this reaction, of course, hydrogen migration occurs to yield t-butyl-alcohol. If, indeed, migration proceeds through a factor corresponding to Taft's pi complex, the observed product will consist almost entirely of olefin, and any alcohol which appears will be formed from hydration of the isobutene produced and will hence contain D.

Since approximately 60% of t-butylalcohol resulted along with only 20% of total olefin at 99° and an even greater yield of alcohol at lower temperatures, and since no D was incorporated into the alcohol it is quite safely concluded that the pi complex, if such a structure exists, is unequivalent to the bridged protonium ion of carbonium ion rearrangements.

The attempted rationalization is that in the former the quite diminutive proton is embedded in the pi cloud of the olefin, whereas in the latter the H is at all times bonded by sp^3 orbitals on the two contiguous carbons and represents, most probably, a transition state (energy maximum). However, since the structures involve identical nuclear arrangements, and since the pi complex purports to represent an intermediate of some stability, it would seem this would indeed be favored as the reaction coördinate in hydride shifts.

SUMMARY

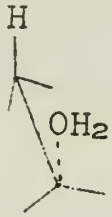
It is the opinion of this writer that, in actual fact, no compelling evidence for a pi complex intermediate in the hydration of olefins has been adduced, and that the simplest mechanism quite adequately fits the observed data. Indeed, more compelling evidence is advanced for the non-existence of such an intermediate in the form of its non-identity with the bridged protonium ion. To epitomize, the transition state for olefin hydration must be considered as resulting from direct hydronium ion attack on the olefin, and most probably involves a quite weak O-H bond to the leaving water molecule and a similarly attenuated bond to the nucleophilically participating, entering water molecule. However, no bonding of the latter type is specifically required by the data at hand.



It is pertinent, then, in this connection, that a pi complex intermediate need not be invoked to explain the observed trans addition of HBr to olefins, for it would be quite objectionable to omit it in the one reaction and not in the other. It need only be observed that only in trans addition does a completely staggered molecule result. Cis addition provokes all bonds into eclipsed positions. It does not ensue from this argument that a quite concerted addition is requisite in order to observe trans addition. It is probable that most of these

additions incur at least a small nucleophilic involvement, but even this is not required. It is only necessary that the quite reactive carbonium ion attack a water molecule before rotation occurs about the C-C bond being added across.

Trans addition



Cis addition

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OMMOCHROMES

Reported by J. F. Porter November 7, 1957

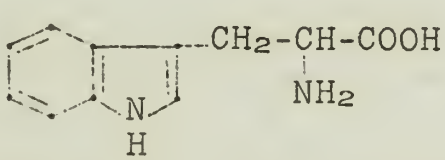
Ommochromes are a class of natural pigments found in the bodies of many arthrapods. Their occurrence was first noticed in flies of the genus Drosophila, and they owe their name to the fact that they are found in the ommatida or elongated eye cells of several insects.

The first insights into their nature came from genetic studies (1). It was known that the genes of an organism were responsible for its individual characteristics. The method of action of the genes; the mechanism of the linkage between the gene and the characteristics of the organism, was not known. Two methods seemed possible. The action of the genes could be confined to a single cell, or the genes could produce diffusable products which could affect many cells. These products could be formed in the original cell and then could determine the nature of the cells subsequently formed. Experiments were run to test the latter hypothesis.

At least two mutant strains of Drosophila melanogaster are knowns which have colorless eyes. The strains differ in their external coloring. Organs from wild members of the species (whose eyes are colored) were surgically implanted in flies with colorless eyes. The eyes of the mutant species became colored, showing that the eye coloring could be brought about by a diffusable substance. It was later found that an extract could be prepared by treating dried pupae of wild flies with hot water. This extract produced eye coloration when injected into or fed to flies with colorless eyes (2). Tissue was also surgically transferred between members of the two mutant strains (3). Tissue from one strain, called the cinnabar or CN strain, brought no color to the eyes of the other (vermillion or V) strain. Tissue or extracts of the V strain caused eye coloration in members of the CN strain. Crossbreeds containing genes from both V and CN strain had colored eyes.

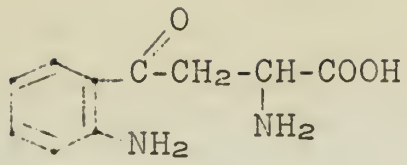
It was also known (4) that wild flies grown on a peptone-glucose dict containing no tryptophane developed no eye coloration. It seemed possible that the eye pigment was a product of tryptophane metabolism and was formed by the catalytic action of at least two different genes:

tryptophane —V gene→ V material (the material which can be extracted from V pupae)



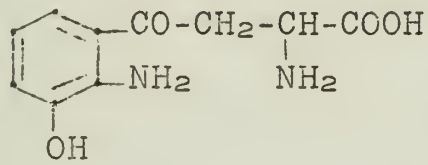
—CN gene→ CN material

The V material was found to be kynurenine (5):



This known substance had been found in canine excretions. It had been shown to be a product of tryptophane metabolism by injecting large quantities of tryptophane into dogs. When this was done a great increase in the amount of kynurenine produced was noticed (6). Kynurenine produced the same eye-coloring effects in Drosophila melanogaster as the V material extracts (5).

It was found that eye pigment formation continued was when the eyes were removed from the rest of the body. This process was inhibited by cyanide ion. Since cyanide is an inhibitor of several oxidizing enzymes it was believed that the process of pigment formation contained an oxidation step. Oxidation products of kynurenine were therefore examined. 3-Hydroxykynurenine was found to have the same effect as the CN material (7).



3-hydroxykynurenine

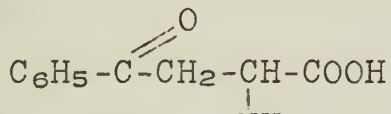
Extracts were made of the naturally occurring pigments by E. Becker (8). He believed that ommochromes were a hitherto unrecognized class of natural pigments, characterized by their insolubility and unusual relax behavior. The bright red extracts which he prepared could be reduced to a yellow form. The red color could be regenerated by allowing the extracts to stand in the air for a few minutes.

Crude preparations of the natural pigments were fractionated by paper chromatography and were found to contain a mixture of dyes (9). At least four separate pigments were found to be present, and were given the names xanthommatine, rhodommatine, ommatine C and ommatine D. Xanthommatine was later isolated as a crystalline compound. Ommatine C could be isolated only after the extracts were allowed to stand for several days and was not found in freshly prepared extracts. It may therefore be a degradation product of one of the other pigments. All four pigments were found to be labeled when C^{14} labeled kynurenine or 3-hydroxykynurenine was injected into the original organism (10,11).

The available amounts of the natural pigments were not large enough for ordinary derivative analysis. The solubility of the pigments was also quite small, and they were found to be unstable to alkali (9). The color of a xanthammatin solution was found to fade within a few hours at pH 8.5 and 20°. The loss of color was more rapid at higher pH. Studies were made of model compounds in an attempt to determine the chemical nature of the natural pigments.

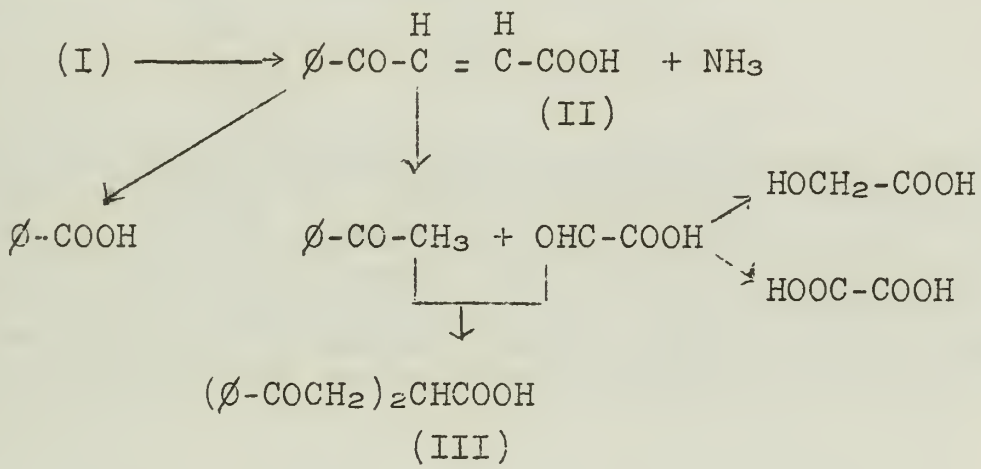
It seemed possible (11) that if the dyes are derivatives of 3-hydroxykynurenine the reactions with alkali may yield the same products, especially if 3-hydroxykynurenine is formed as the first step in the hydrolysis of the dyes. Rhodommatine, xanthommatin,

and 3-hydroxykynurenine were therefore treated with alkali and the reaction mixtures were acidified and fractionated by paper chromatography. To examine the behavior of the side chain of 3-hydroxykynurenine a second model compound was also treated with base:



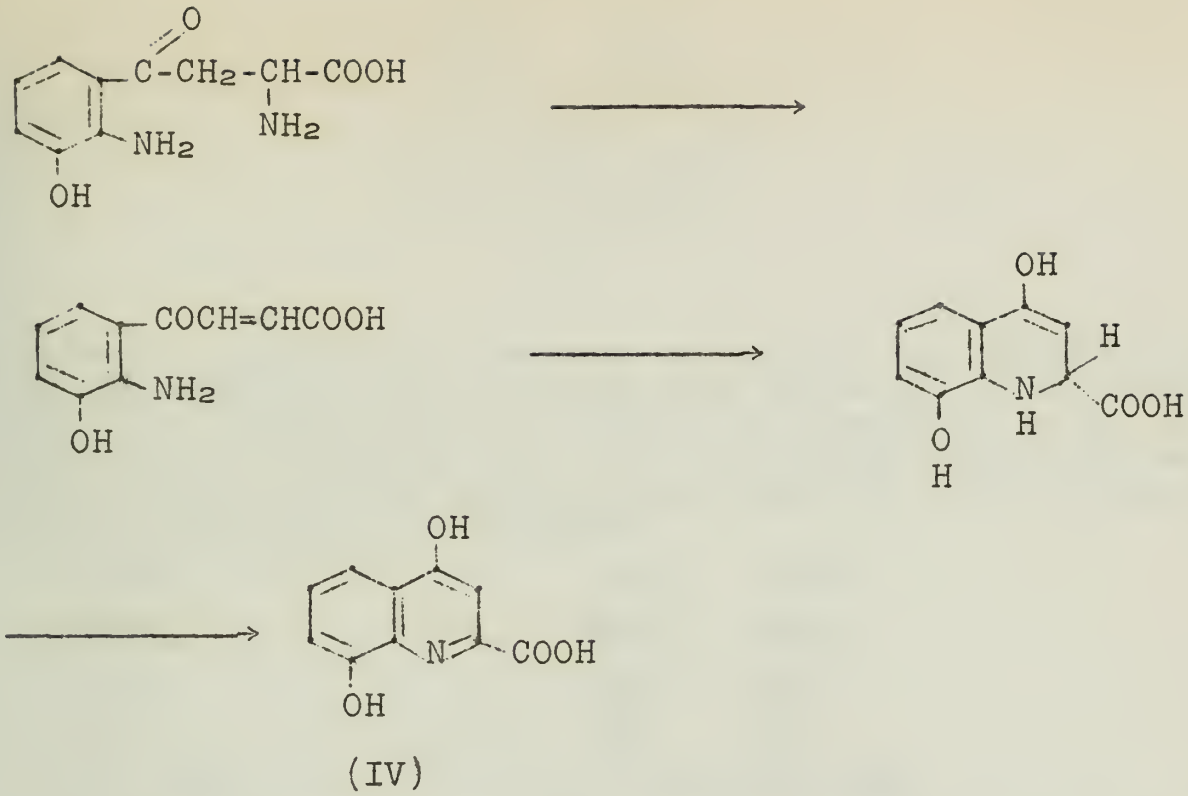
(I)

From the reaction mixture of (I) were isolated acetophenone, diphenacyl acetic acid and oxalic acid. By paper chromatography a ninhydrin positive substance was also isolated. The Rf value of this substance was the same as that of a substance which was found in the reaction mixtures of xanthommatin, rhodommatin, and 3-hydroxykynurenine. The observed products of the hydrolysis of (I) were explained by the following set of reactions:



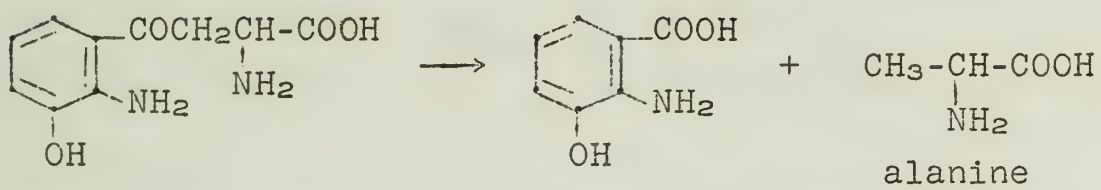
This hypothesis was supported by the observations of Pechman who found that β benzoyl acrylic acid (II) yielded acetophenone and glyoxylic acid on treatment with base (17). It was also known that (III) could be formed from acetophenone and glyoxylic acid (14). The formation of the ninhydrin positive substance was not explained but was believed to be due to the reaction of ammonia with one of the other products.

The treatment of 3-hydroxykynurenine with buse gave similar products. An additional product was crystallized from the reaction mixture and found to be xanthurenic acid (IV). This known compound had previously been prepared synthetically (15). The reaction proposed for its formation were



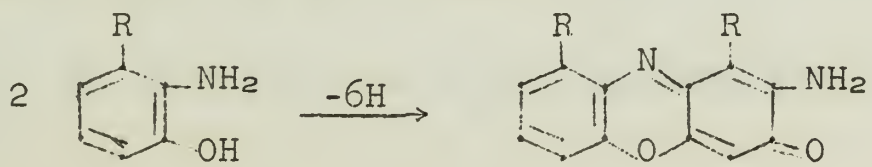
(IV)

It now seemed certain that rhodommatine and xanthommatine were structurally similar to 3-hydroxykynurenine. The question was raised as to whether xanthurenic acid is built into the xanthommatine molecule or is formed from it by a process similar to its formation from 3-hydroxykynurenine. Xanthommatine and rhodommatine were treated with the enzyme kynureninase. This enzyme attacks α-amino-γ-keto acids and splits off alanine (16) in a reaction similar to:

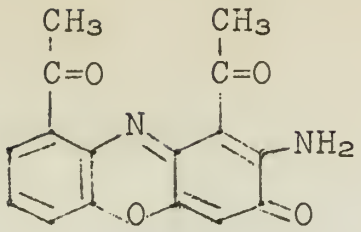


Alanine was split from the natural pigments, showing that a free α-amino acid side chain was present.

It was previously mentioned that pigment formation from 3-hydroxykynurenine was believed to be an oxidative process. It was also known (17) that 3 aminophenoxazones could be formed by oxidation with potassium ferricyanide from 2-aminophenols with no substitution in the 5 position:

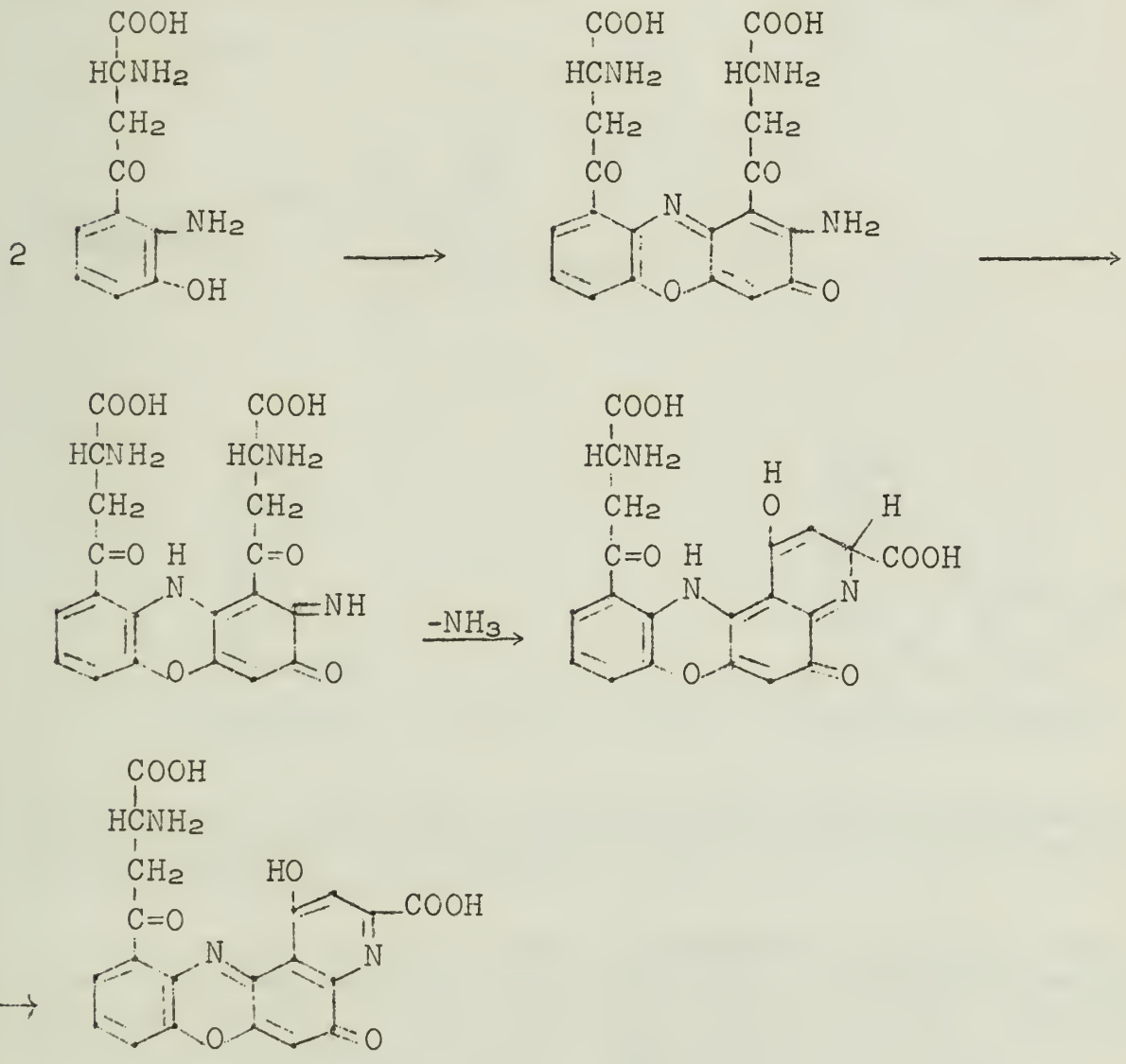


Since 3-hydroxykynurenine was hard to obtain, a similar compound, 2-amino-3-hydroxyacetophenone was first studied (12). Treatment with potassium ferricyanide caused an almost immediate oxidation. The compound produced was found to be V.

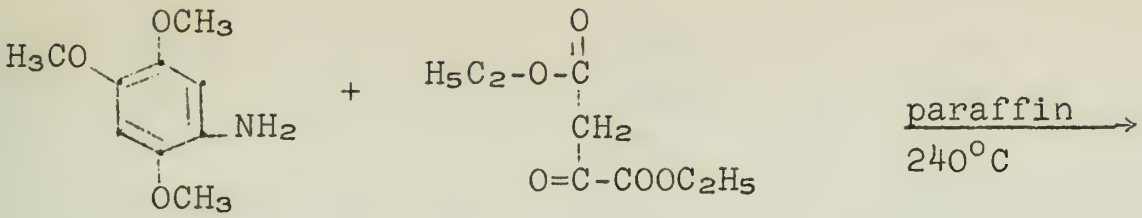


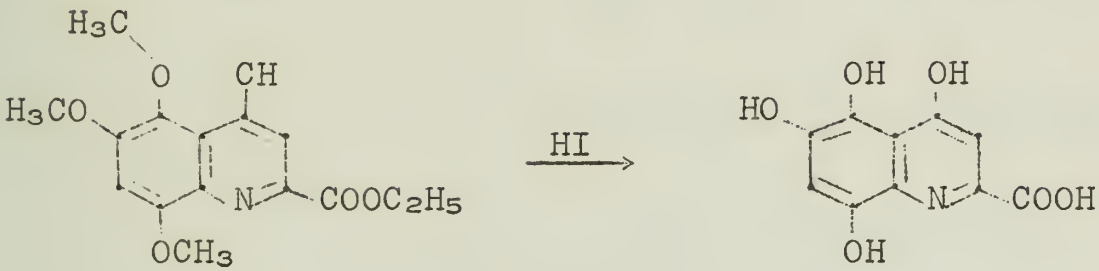
(V)

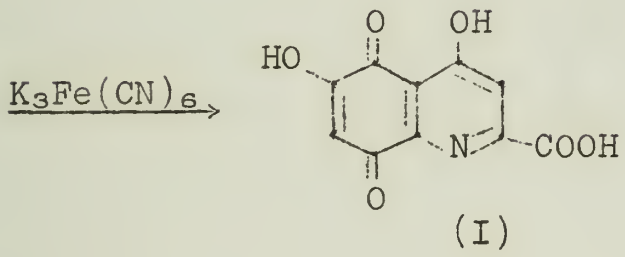
Its redox behavior was the same as that of the natural pigments. If 3-hydroxykynurenine is oxidized with potassium ferricyanide a product is formed which is found to be identical in all respects with natural xanthommatine. If it is assumed that the reaction goes in the same direction as the model compounds the following reaction scheme can be postulated:



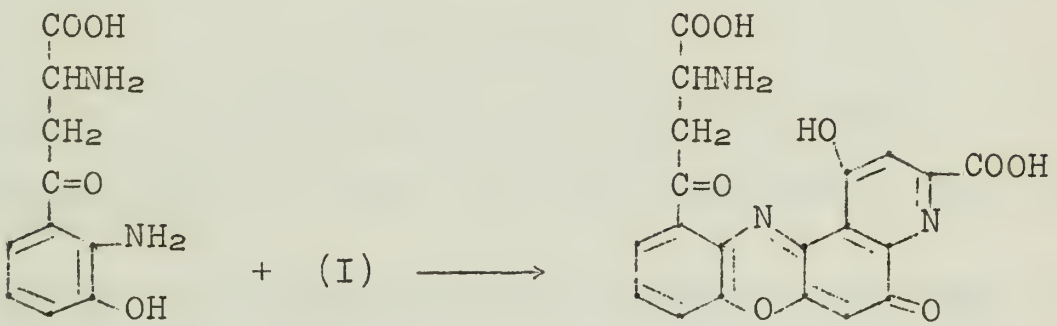
The structure was proven conclusively by a total synthesis (18):





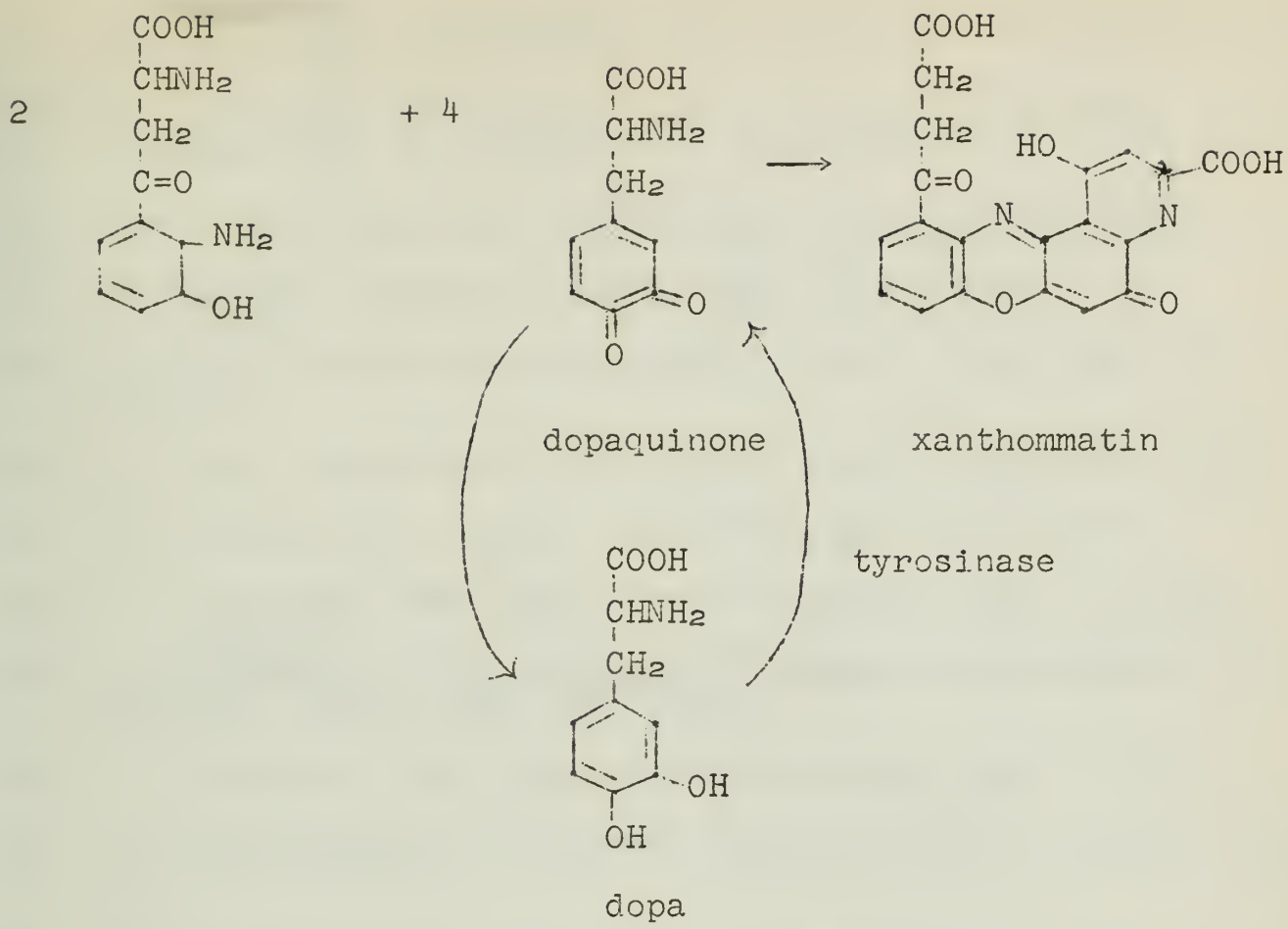


(I)



It was found that the oxidation of the model compound 2-amino-3-hydroxyacetophenone could be brought about by the enzyme tyrosinase in the presence of catechol.

It may be assumed that xanthommatine may be produced *in vivo* from the condensation of two molecules of hydroxykynureine by a process similar to that observed with the model compounds (19). It has been suggested that dopa, present in abundance in animal tissue, may function as the tyrosinase substrate:



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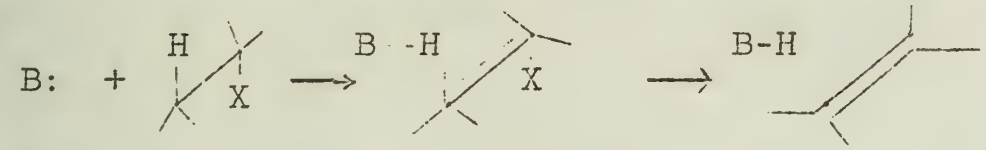
MECHANISMS OF BASE-PROMOTED ELIMINATION REACTIONS

Reported by S. H. Metzger, Jr. November 11, 1957

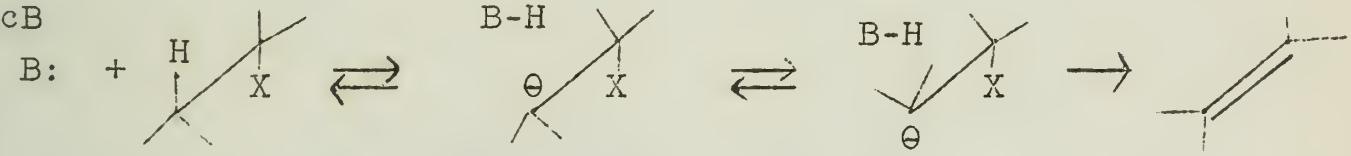
INTRODUCTION

In 1952 Corey (1) presented a seminar on the duality of mechanism for base-promoted second order elimination reactions.

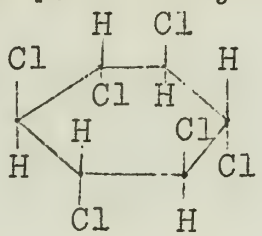
E2



ElcB



The second mechanism [labeled ElcB by Ingold (2a)] was proposed by Cristol on the basis of cis-elimination of hydrogen chloride from β-benzenehexachloride (I) [See Corey (1)].



I

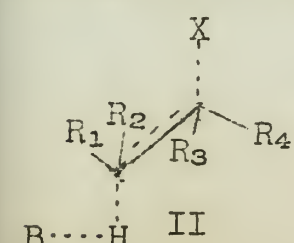
Since Cristol's proposed two-stage mechanism, a large amount of work has been expended in investigations of base-promoted eliminations, both trans and cis. These investigations may be divided into four parts.

1. Elucidation of the geometry of and electron distribution in the transition state of trans-eliminations.
2. New examples of cis-eliminations.
3. The mechanism of cis-eliminations.
4. Steric effects - factors which influence the direction of elimination (Hofmann or Saytzeff).

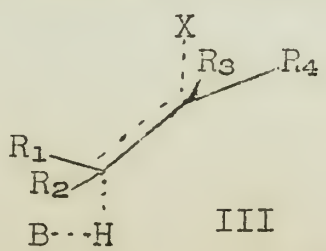
This seminar will review only the more important work from 1953 to the present.

Geometry of The Transition State of E2 Reactions

In the limiting cases the transition state of base-promoted trans-eliminations may resemble starting material (II) or product (III).



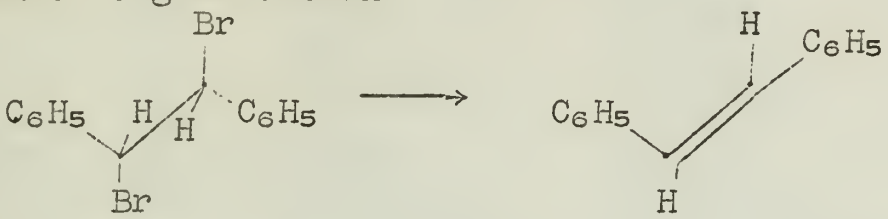
II



III

Needless to say, there is a spectrum of intermediate geometries.

Curtin (3) has pointed out that E2 eliminations are subject to the "cis effect". For example phenylbenzylcarbinyl triethylbenzoate [R_1=R_4=C_6H_5, R_2=R_3=H, X=-$CO_2C_6H_2(C_2H_5)_3$] yields about 100 times more trans-stilbene than cis-isomer. When treated with iodide ion in acetone meso-stilbene dibromide reacts at least 100 times as fast as the dl-isomer to give olefin.

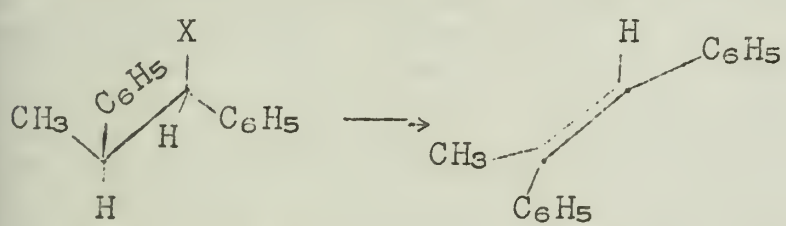


meso

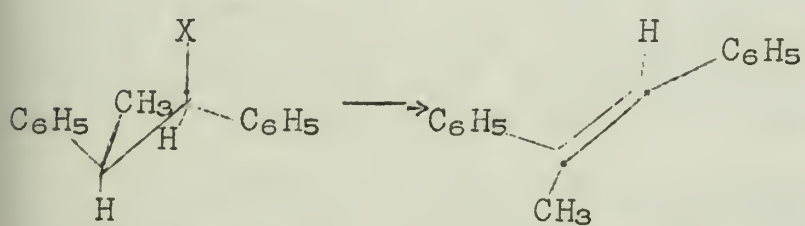
dl

Curtin (3) calculated the free energy difference of the transition state of the two isomers to be about 4.2 kcal. This is a measure of the "cis effect" in the transition state. By comparison, the energy difference between cis- and trans-stilbene is 5.7 kcal. (heats of hydrogenation).

Cram, Green, and Depuy (4) studied the effect of base strength, leaving group, and solvent on the geometry of the transition state in E2 reactions. They utilized the following diastereoisomers (IV and VI) and obtained 90 - 100% yield (U.V.) of olefin in all reactions.



IV (erythro) V



VI (threo) VII

Table I (4)

Ratios of Elimination Rates of Diasteromeric 1,2-Diphenyl-1-propyl-X

No.	X	Temp, °C	Solvent	Base	k_2 threo / k_2 erythro
1.	Br	50	C_2H_5OH-C_6H_6	C_2H_5ONa	0.7
2.	Cl	50	C_2H_5OH	C_2H_5ONa	1.1
3.	Br	50	$(CH_3)_3COH$	$(CH_3)_3COK$	5.4
4.	Cl	50	$(CH_3)_3COH$	$(CH_3)_3COK$	15
5.	$^{\oplus}N(CH_3)_3$	75	C_2H_5OH	C_2H_5ONa	57
6.	Cl	75	C_2H_5OH	C_2H_5ONa	1.0
7.	Cl	75	n-$C_8H_{17}OH$	n-$C_8H_{17}ONa$	0.9
8.	Cl	75	n-$C_6H_{13}CHOHCH_3$	n-$C_6H_{13}CHOKCH_3$	3.5
9.	Cl	75	C_6H_6	n-$C_6H_{13}CHOKCH_3$	~ 5
10.	Cl	75	$(CH_3)_3COH$	$(CH_3)_3COK$	10.6
11.	Cl	75	$(CH_3)_3COH$	C_2H_5OK	~ 4
12.	Cl	75	$C_2H_5(CH_3)_2COH$	$C_2H_5(CH_3)_2COK$	10.7
13.	$^{\oplus}N(CH_3)_3$	30	$(CH_3)_3COH$	$(CH_3)_3COK$	1.1

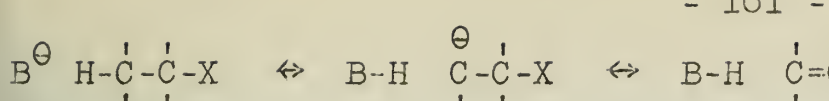
All the runs gave products expected from trans-elimination except No. 13 in which both the erythro (IV) and threo (VI) isomer gave the trans-olefin (VII). This anomaly might be interpreted as a possible two-stage cis-elimination, but a more likely explanation is that the strong base caused a rapid epimerization at C_α, followed by trans-elimination. Compounds IV and VI could not be equilibrated; the corresponding diastereomeric formates were equilibrated in formic acid giving a threo/erythro ratio of 0.82 (5). Cram concluded that the diastereomeric bromides or chlorides should be of about the same stability (almost equal energy) since the bulk of the halides is about the same as the formate.

If Cram's postulate that IV and VI are of about equal stability is correct, then his data present somewhat of a contradiction to the magnitude of the "cis effect" in the transition state shown by Curtin and others. For in No. 1, 2, 6, 7 (Table I) there is no "cis effect" in the transition states since the rates of the threo- and erythro-isomers are about equal. A detailed analysis of this difference is too involved to include here, but it may be said, in general, that it appears as if the transition states in Cram's systems resemble III to a much less degree than the transitions states in the examples cited by Curtin (3). In this connection, it is interesting to note that in some earlier work (6) it was found that IV (X=Cl) would not undergo elimination with dl-potassium-2-octylate in benzene at 80° compared to good yields of the expected products from IV (X=Br, I) and VI (X= Cl, Br, I) (Compare with No. 9.)

On a relative basis the k_2 threo/k_2 erythro ratios represent the magnitude of the "cis effect" under various conditions. If we assume that a change of conditions changes the geometry of the transition state of both isomers in the same direction, then the higher the rate ratios, the more the transition states resemble product (III). The very large effect of the quaternary ammonium salt is somewhat puzzling.

Electron Distribution In the E2 Transition State

The following resonance structures may be said to contribute in varying degrees to the structure of any transition state in a trans-elimination.



VIII IX X

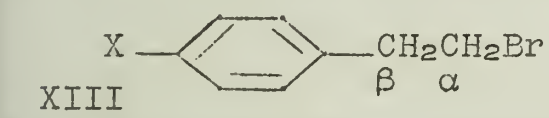
Several investigators have studied the charge distribution in the transition state by application of the Hammett equation to elimination reactions. Since ρ is a measure of the change in charge from the ground state to the transition state [for a full discussion see Swain and Langsdarf (7)], the value of ρ for elimination reactions will always be positive. The magnitude of this positive value gives a good indication of the charge distribution in the transition state.

The first applications of the Hammett equation to E2 reactions were the determination of ρ values for XI (ρ=2.729) and XII (ρ=2.456) and for substituted β-phenylethylchloride (9).

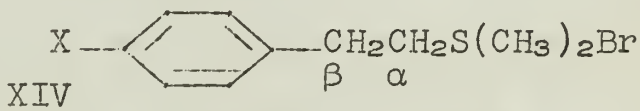
$ArCHCCl_3$ $Ar_2CHCHCl_2$

XI XII

A more extensive investigation was recently made by Saunders and Williams (10) on trans-eliminations from XIII a-f and XIV a-d with



XIII



XIV

a, X=H; b, X=CH_3; b, X=CH_3O; d, X=Cl; e, X=CH_3CO; f, X=NO_2

sodium ethoxide in absolute ethanol at various temperatures. In all experiments the yields of olefin were quantitative (U.V.).

Table II

Rate Constants at 30°

Cmpd		$k_2 \times 10^5$ l. mole^{-1} sec^{-1}
XIII	a	41.7
	b	22.8
	c	16.2
	d	191
	e	3720
	f	74200
XIV	a	1970
	b	232
	c	111
	d	2440

Table III

Hammett Correlation of Elimination Rates

Cmpd	ρ (a)
XIII a-d	2.154 ± 0.242
XIII a-f (b)	2.342 ± 0.115
XIII a-f (c)	3.505 ± 0.338
XIV a-d	2.639 ± 0.157

(a) Calculated by method of least squares.
(b) σ^*(11)values for p-nitro and p-acetyl.
(c) normal σ value.

Examination of Table III tells us first of all that in the transition state of the systems studied a large proportion of the negative charge resides on C_β, and thus, the charge distribution of the transition state more nearly resembles that of IX. The predominance of the charge on C_β is further supported by the observation that σ^* values (11) for p-nitro and p-acetyl fit the data better than normal σ values. Furthermore, the proportion of negative charge on C_β is greater for the series in which the sulfonium salt is the leaving group than for the series in which bromide is the leaving group. This is to be expected since the sulfonium salt contains a poorer leaving group than the bromide and activates the β-hydrogen by induction.

It should be remembered in examining Table II that although a high proportion of charge resides on C_β, the stereospecific nature of E2 eliminations dictates that there must be some degree of double-bond character between C_α and C_β, however small. Then, it is just a matter of competition as to the relative importance of stabilization of charge or stabilization of the incipient double bond as factors in effecting the rate constant. It is, therefore, not suprising in the system studied that electron-contributing para-substituents, which would be expected to increase k_2 due to resonance stabilization of the incipient double bond, actually decrease k_2 in comparison to electron-withdrawing substituents. Resonance stabilization of the negative charge is more important in these compounds. The greater sensitivity of the sulfonium salts to electrostatic effects gives support to Ingold's theory (2b) that Hofmann-type eliminations are a result of polar effects of the onium salts.

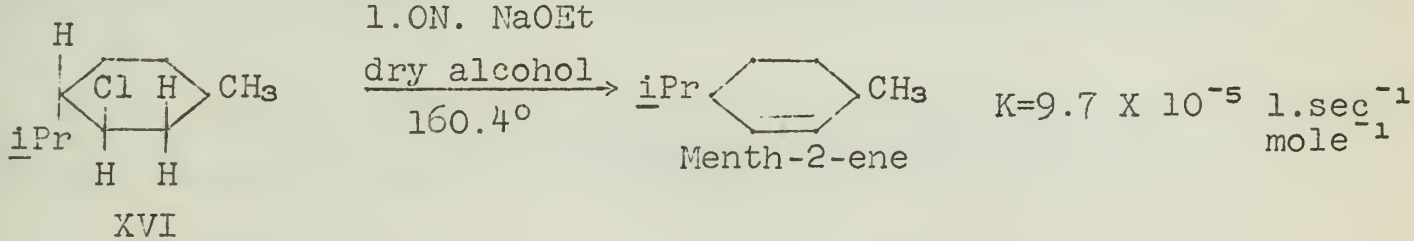
Depuy and Froemsdorf(12) conducted a similar investigation to that of Saunders and Williams and obtained essentially the same results.

Further support for a high proportion of negative charge on C_β (IX) in certain systems might be offered from the $^{32}S/^{34}S$ isotope effect observed for E2 elimination from 2-phenylethyl-dimethyl-sulfoniumbromide (XV)(13). As compared to a value of 1.8% obtained for an SN1 displacement from t-butyldimethylsulfonium iodide, an isotope effect $[(k_{32}/k_{34}-1) \times 100]$ of only 0.15% was observed for the elimination reaction from XV. This was interpreted to mean that in the transition state of the E2 reaction of XV, there is little stretch to the carbon-sulfur bond. Therefore, it was concluded that most of the negative charge resides on C_β.

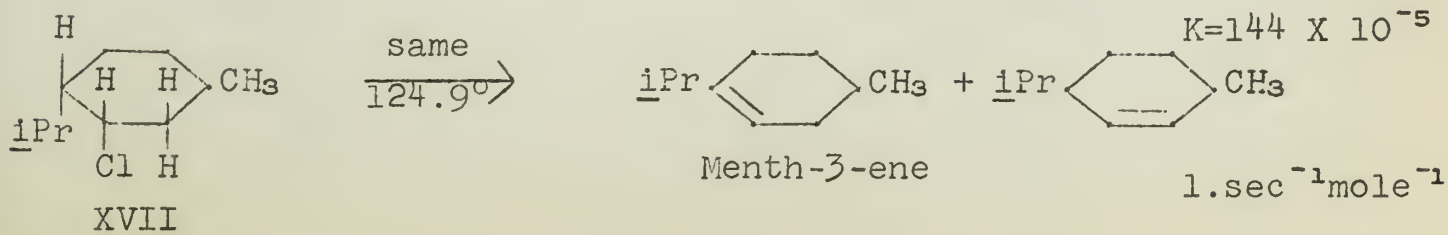
Cis-Eliminations: New Examples

If cis-eliminations are to be observed, the best system to use would be cyclic reactants in which the hydrogen on C_β and the substituent on C_α can be held in a fixed cis (or trans) configuration. It will be profitable to consider one or two examples in which cis-elimination is possible, but was not observed.

Hughes, Ingold, and Rose (14), in an investigation of the kinetics and products of eliminations from menthyl- (XVI) and neomenthyl chloride (XVII), obtained the following results.



XVI

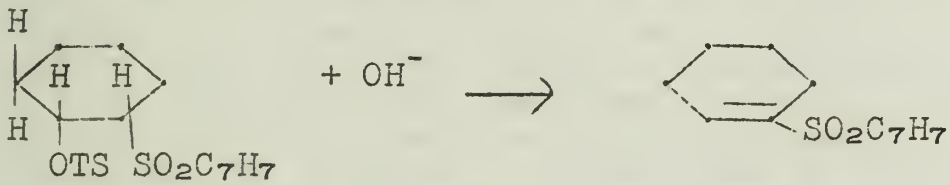


XVII

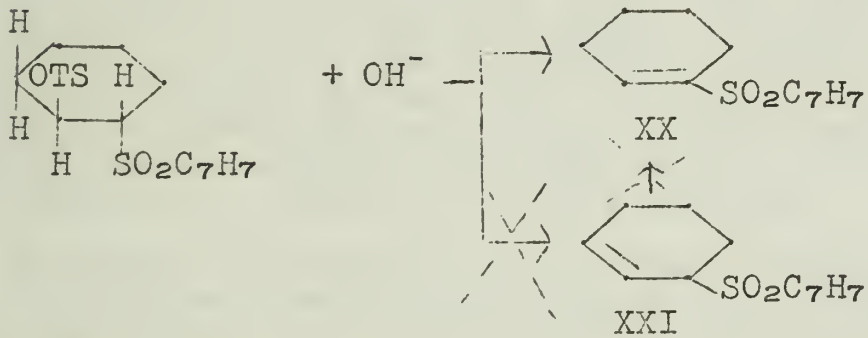
No cis-elimination was observed from XVI, even though the 3-olefin should be favored due to hyperconjugation, and even though the rate of trans-elimination from XVI is depressed (as compared to cyclohexyl chloride) due to the necessity of the chloride and isopropyl group to assume the more unstable trans-axial conformation.

Further negative evidence for cis-elimination in certain compounds is the dehydrobromination of cis-1,2-dimethyl-1-bromocyclohexane to give chiefly 2-methylene-2-methylcyclohexane (15).

Bordwell and Kern (16) snythesized the cis (XVIII) and trans (XIX) isomers of 1-p-tolylsulfonyl-2-tosyl derivatives of hexane. Reaction of the two isomers with potassium hydroxide in a water-dioxane mixture at 20° gave the product (XX) expected from trans-elimination from XVIII, but XVI underwent exclusively cis-elimination to give XX. Similar results were obtained for the cyclopentane series.

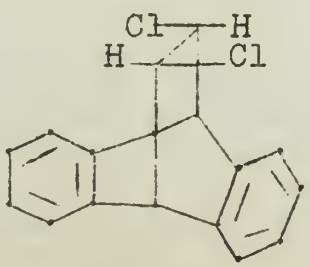


XVIII XX

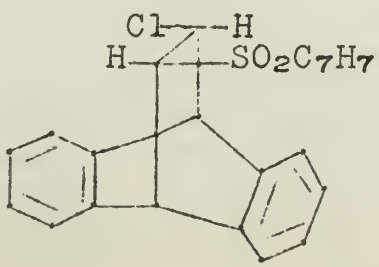


A synthetic sample of XXI did not rearrange to XX under the reaction conditions. All rates were second order and k_2 for XIX increased with decreasing water in the dioxane-water mixture, a phenomenon which is consistent with the generalization made by Ingold (2c) for the effect of solvent on this type E2 reaction. It may be concluded that second-order cis-eliminations do take place, even though trans-eliminations might be possible, if the β-hydrogen is made sufficiently acidic by strong inductive groups.

It has already been mentioned in the introduction that β-benzene-hexachloride undergoes cis-elimination of hydrogen chloride. Similarly compounds XXII (17) and XXIII (18) undergo exclusively



XXII



XXIII

cis-elimination when treated with base in alcohol-dioxane solvent. The substitution of the p-tolylsulfonyl group for chloride on C_α increases the rate by about 10^{10} (18). Thus, although very slow, cis-eliminations may occur with systems (XXII) where the β-hydrogen is not activated, but in which trans-elimination is highly retarded or impossible. Strong activation of the β-hydrogen in such systems (XXIII) tremendously increases the rate of reaction [a similar increase was noted for the corresponding trans-eliminations for the cis-isomers of XXII and XXIII (17,18)].

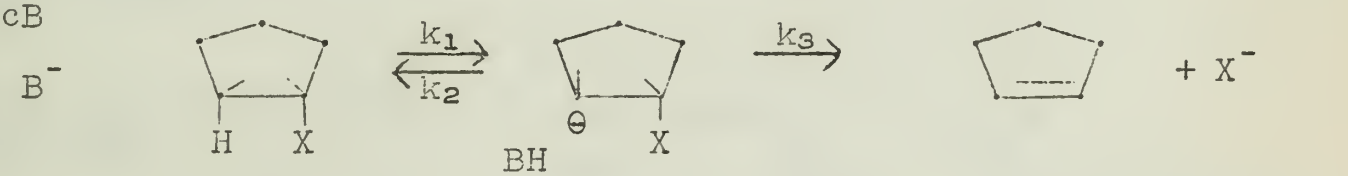
There are several other examples of second order, base-promoted cis-eliminations in the literature (19, 20, 21, 22, 23). A cis-1,4-conjugate elimination has also been investigated (24).

Mechanism of Cis-Eliminations

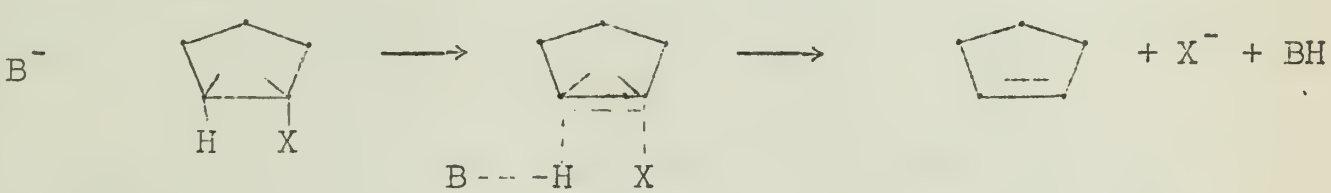
The energy of activation for cis-elimination of hydrogen chloride from β-benzenehexachloride was found to be about 31 kcal., as compared to an average value of about 20 kcal. for trans-elimination from the other isomeric benzenehexachlorides (1). Hughes, Ingold, and Pasternak (25) confirmed these results. The general tendency of activation energies for cis-eliminations to be high (31 - 32 kcal.) for systems in which there is no activation of the β-hydrogen has been confirmed by measurements of the activation energies for cis-elimination from trans-2,3-dichloronorbornane (22) and from trans-β-bromo-styrene (23). The large differences in activation energy for cis- and trans-elimination disappear when one goes to systems where the β-hydrogen is highly activated as is shown, for example, in the 15.6 kcal. and 16.3 kcal. obtained for elimination from XXIII and its cis-isomer, respectively. Other similar examples may be cited (16, 23, 26) for low (12 - 18 kcal.) and approximately equal activation energies.

To explain the above results three mechanisms for second-order cis-elimination have been proposed in the literature, two of which are illustrated below utilizing a cyclopentyl derivative.

M-1 ElcB



M-2 Concerted cis-elimination



In addition, Hughes and Ingold (25) have proposed that in the cis-elimination of hydrogen chloride from β-benzenehexachloride the extra energy of activation (11 - 12 kcal.) is required partly to twist H and X into a more anti-configuration and partly to force the mechanism against the still imperfect trans-orientation (a trans cis-elimination). The two mechanisms illustrated above represent energetically unfavorable paths, as compared to trans-elimination, so long as the β-hydrogen is not highly activated.

In discussing M-1 there are two possibilities to consider: 1) rapid equilibrium between starting material and carbanion with formation of product from the carbanion being the rate controlling step ($V_2 \gg V_3$); 2) a situation where there is essentially no reversible reaction of carbanion to starting material ($V_3 \gg V_2$).

The first possibility for M-1 has been discounted on the basis of deuterium exchange experiments (27, 28, 29) in which no deuterium exchange (or very little) was observed when conducting the eliminations in oxygen-deuterated solvents, with oxygen-deuterated bases, or both. Further evidence was obtained by Weinstock, Pearson, and Bordwell (30) by using a kinetic approach (31). Both the cis- and trans-eliminations from 2-p-tolylsulfonyl-cyclohexyl- and 2-p-tolylsulfonyl-cyclopentyl-p-toluene sulfonates were studied using trimethyl- and triethylamine in 50% aqueous dioxane at 25°. The bases were used in large excess, and the solutions were buffered by some of the amine salts. In all determinations the pseudo first-order rate constants observed increased as more amine was added (general base-catalyzed). It can be concluded that no rapid equilibrium existed between starting material and carbanion since such a mechanism would have been observed to be specific base-catalyzed. Weinstock did concede, however, that if $V_3 \gg V_2$ then an intermediate carbanion of very low stability might be possible. Rough calculation (30) on the basis of the kinetic results gave an upper limit on the mean life-time of the carbanion at about 10^{-9} seconds in the systems studied.

Cristol and Fix (29) have interpreted the deuterium exchange experiments as support for M-1 in which $V_3 \gg V_2$. In their treatment of β-benzene hexachloride with sodium ethoxide in oxygen-deuterated ethanol, they obtained by mass-spectroscopy only about 0.08 excess atom per cent deuterium in the unreacted halide.

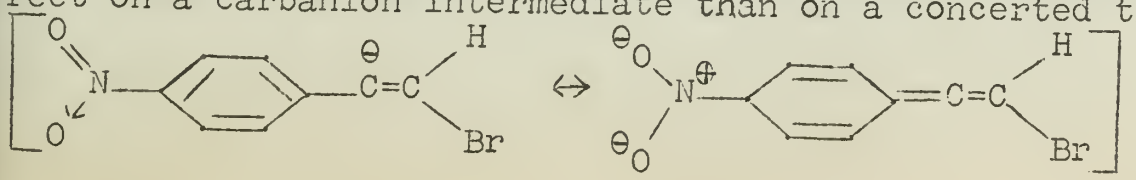
Cristol and Norris (23) continued the argument for a carbanion intermediate from interpretation of the results obtained from a kinetic study of eliminations from cis- and trans-β-bromostyrene and cis- and trans-p-nitro-β-bromostyrene with sodium hydroxide in isopropyl alcohol.

Table IV

Rate Constants and Quantities of Activation at 43°.

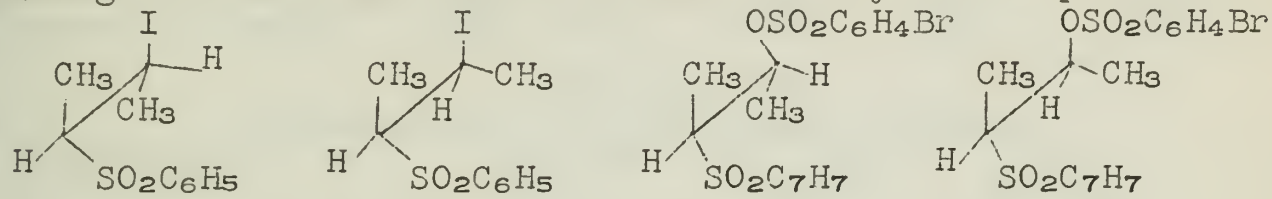
β-Bromostyrene	k l./mole/sec.	k_{cis}/k_{trans}	E_a kcal/mole	$\Delta S^{\ddagger}$ cal./mole/degree
cis-p-nitro	3.71×10^{0}	1.6×10^{4}	17.1	-4.0
trans-p-nitro	2.36×10^{-4}		21.3	-10.0
cis-	3.00×10^{-3}	21×10^{4}	21.1	-5.6
trans-	1.4×10^{-8}		31.8	+4.0

The lower k_{cis}/k_{trans} ratio for the p-nitro series than for the unsubstituted series and the differences in E_a values were interpreted on the basis that the p-nitro group should have a greater stabilization effect on a carbanion intermediate than on a concerted transition state.



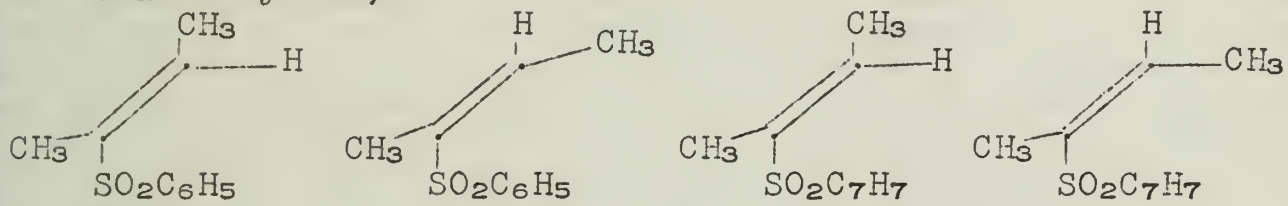
It is felt that the data could have been equally satisfactorily interpreted on the basis of a concerted transition state with a large proportion of negative charge on the benzyl carbon [refer to the work of Saunders (10) and Depuy (12)].

Further work in the field (26,32) took the obvious direction of running eliminations with diastereomeric acyclic compounds



dl-erythro XXIV | dl-threo XXV | dl-erythro XXVI | dl-threo XXVII

which are designed to encourage carbanion formation, but which give cis-and trans-olefin products of practically equal stability (compare with Cram's system).



XXVIII | XXIX | XXX | XXXI

If a carbanion intermediate were formed during the elimination a mixture of products would be expected (non-stereospecificity as proof of an intermediate).

Skell and McNamara (32) reacted one pure solid isomer (either XXIV or XXV) and a mixture of isomers with pyridine in boiling benzene. The infrared spectra of the olefins formed showed a pure isomer (XXVIII or XXIX) from the pure starting material and a mixture of isomeric olefins from the mixed starting materials. Bordwell and Landis (26) reacted pure XXVI and XXVII with trimethylamine or hydroxide ion in 50 % aqueous dioxane and obtained XXX and XXXI, respectively. In both experiments the trans-stereospecificity observed eliminated the possibility of a stable carbanion intermediate. An alternate explanation (32) was offered in that a carbanion might be formed if it looses the leaving group about ten times as fast as it suffers rotation about its central bonds. Since the rotation rates are about 10^{-8} to 10^{-12} sec^{-1} depending upon the barrier to rotation, the life-time of such a carbanion would have to be less than 10^{-9} sec. (32) [this value is in agreement with Weinstock's calculation (30)].

To accept this alternative explanation one would have to assume a planar trans-transition state that goes to the short-lived carbanion and thence to product.

A summary of Weinstock and Bordwell's data is presented below.

Table V (16, 20, 33)

Tosylate	Type of Elim.	Relative Rates With OH^-	Relative Rates With Me_3N	Relative Rates With ET_3N	Rate Ratios k_{OH}/k_{Me_3N}	Rate Ratios k_{ET_3N}/k_{Me_3N}
trans-2-tosylcyclohexyl	cis	0.79	0.855	0.135	308	0.068
cis-2-tosylcyclohexyl	trans	81	21.7	15.7	5220	0.324
trans-2-tosylcyclopentyl	cis	11.9	98.5	17.4	169	0.077
cis-2-tosylcyclopentyl	trans	235	118	114	2780	0.435

Table VI (26)
Trimethylamine in 50% Aqueous Dioxane

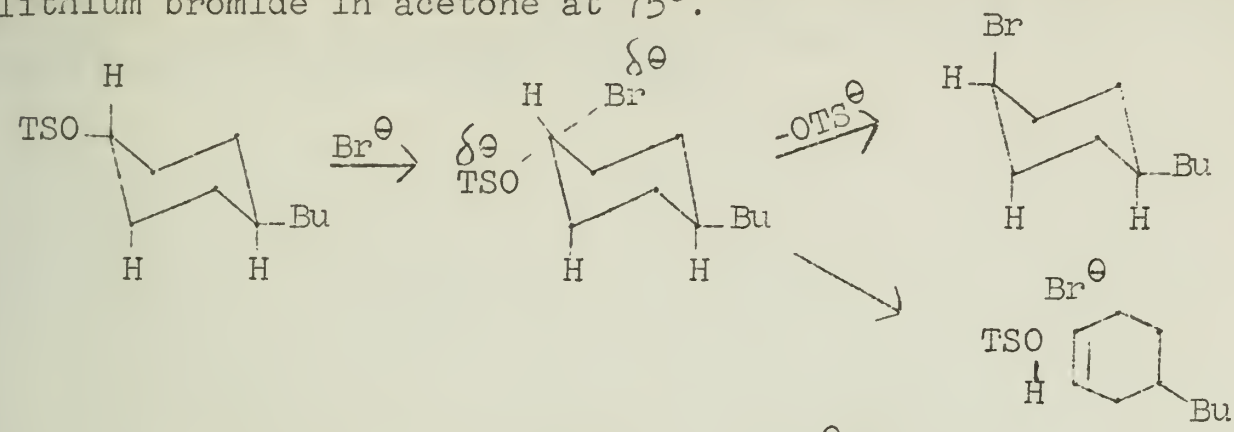
Brosylate	Type of Elim.	Rel. Rate (25°)	E_a, Kcal/mole	$\Delta S^{\ddagger}$ e.u.
threo-2-tosyl-3-butyl	trans	1.0	14.5	-23.6
erythro-2-tosyl-3-butyl	trans	2.3	12.8	-27.6
trans-2-tosylcyclopentyl	cis	7.0	11.8	-26.4
cis-2-tosylcyclopentyl	trans	9.7	12.1	-27.2

The higher values for hydroxide rates than for trimethylamine rates (Table V) are to be expected since hydroxide ion is a stronger base, but it should be noted that the ratios for trans-eliminations are about twenty times the values for the corresponding cis-eliminations. In cis-eliminations the attacking base is much closer to the leaving group than in trans-eliminations. Since the tosylate oxygens are negatively charged, a negatively charged base would be repelled and the transition state made less stable as compared to the stabilization influence of the electrostatic attraction between the tosylate oxygens and trimethylamine, which acquires a partial positive charge in the transition state.

Of considerable interest is that in the cyclopentane series the trans/cis elimination ratios are 20, 6.6, and 1.2 for hydroxide ion, triethylamine, and trimethylamine, respectively (Table V). In the brosylate series the ratio with trimethylamine is 1.4 (Table VI). Weinstock and Bordwell have interpreted the data with trimethylamine to mean that a planar four-centered transition state is of very little importance in providing a favorable reaction path. Thus, in opposition to Cristol, it was concluded (26) from the data above and from the earlier observation of general base catalysis that no energetically unfavorable two-step mechanism exists for cis-eliminations. Some type of concerted mechanism (M-2) for cis-eliminations was proposed. It should be noted that a comparison of the acyclic series with the cyclopentane series is not valid, for a concerted cis-elimination in the acyclic system would require an eclipsed formation.

The discounting of a carbanion intermediate is on sound grounds if based on the experimental evidence that failed to show an intermediate, but the fact that the energy of activation for cis-elimination is not higher than that for trans-elimination is not evidence to eliminate a two-step mechanism. Also, in comparing the rates in the cyclopentane series Weinstock and Bordwell apparently overlooked what could be a large free energy difference in the cis- and trans-isomers of the starting materials. Such a consideration would lead to the conclusion that the transition state for cis-elimination is more stable than that for trans-elimination in the systems studied. The mechanism for cis-eliminations remains to be resolved.

Recently, (34) a novel mechanism was proposed to explain second-order eliminations accompanying SN2 displacement when trans- and cis-4-t-butylcyclohexyl p-toluenesulfonate are reacted with lithium bromide in acetone at 75°.



It was proposed that the leaving group $^{\ominus}$OTS departs with a proton, although removal of a proton by a solvent was not excluded. The E 2 mechanism is essentially precluded by stereoelectronic considerations. An El elimination is precluded by a substantial rate factor between lithium bromide and lithium perchlorate.

Saytzeff versus Hofmann Elimination

According to Ingold (2b) the Saytzeff rule is a result of electromeric factors and the Hofmann rule is a result of polar factors.

The first observation that Hofmann eliminations may be attributable to steric effects may be credited to Schramm (35).

Recently, Brown and co-workers (36, 37, 38, 39, 40, 41) have attempted to show that steric requirements of the alkyl groups on the incipient double bond and the steric requirements of the attacking base and leaving group may effect the direction (Hofmann or Saytzeff) of bimoleculer eliminations. It was shown (36,37) that an increase in the steric requirements of R(R=Me, Et, iPr, and t-Bu) in the tertiary bromides $RCH_2CBr(CH_3)_2$ results in an increased tendency toward elimination by the Hofmann rule [this trend is predictable by a consideration of the magnitude of the "cis effect" in the transition state (3)]. With respect to alkoxide bases (38), a shift from Saytzeff-to Hofmann-type elimination was illustrated in reactions of tertiary amyl bromide with the potassium salts of ethanol, t-butyl alcohol, t-amyl alcohol and triethylcarbinol. Similar shifts were noted in going from pyridine to α-picoline to 2,6-lutidine (39). In eliminations from the 2-pentyl derivative, RX, the per cent 1-olefin (per cent of mixture) increased with the following order of leaving groups (said to be the increasing steric order): $Br \sim I > OSO_2Tol > SMe_2^{\oplus} > SO_2Me > NMe_3^{\oplus}$ (40). Brown concluded that steric factors are more important then polar factors in eliminations of onium salts.

Some support for Brown's work with base may be found in the recent observation (42) that sodium thiophenoxide has greater nucleophilic power than either sodium ethoxide or sodium phenoxide for E2 eliminations from t-butylchloride. Thiophenoxide is the weakest base of the three.

It is felt that Brown presented insufficient data to conclude that base strength is not a major factor in directing eliminations. His belittling of polar effects of onium salts would be strongly debated by Depuy (12) and Saunders (13), who found polar control not only with sulfonium salts but also with bromine as the leaving group in their β-phenylethyl system.

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SCINTILLATION COUNTING FOR ORGANIC CHEMISTRY

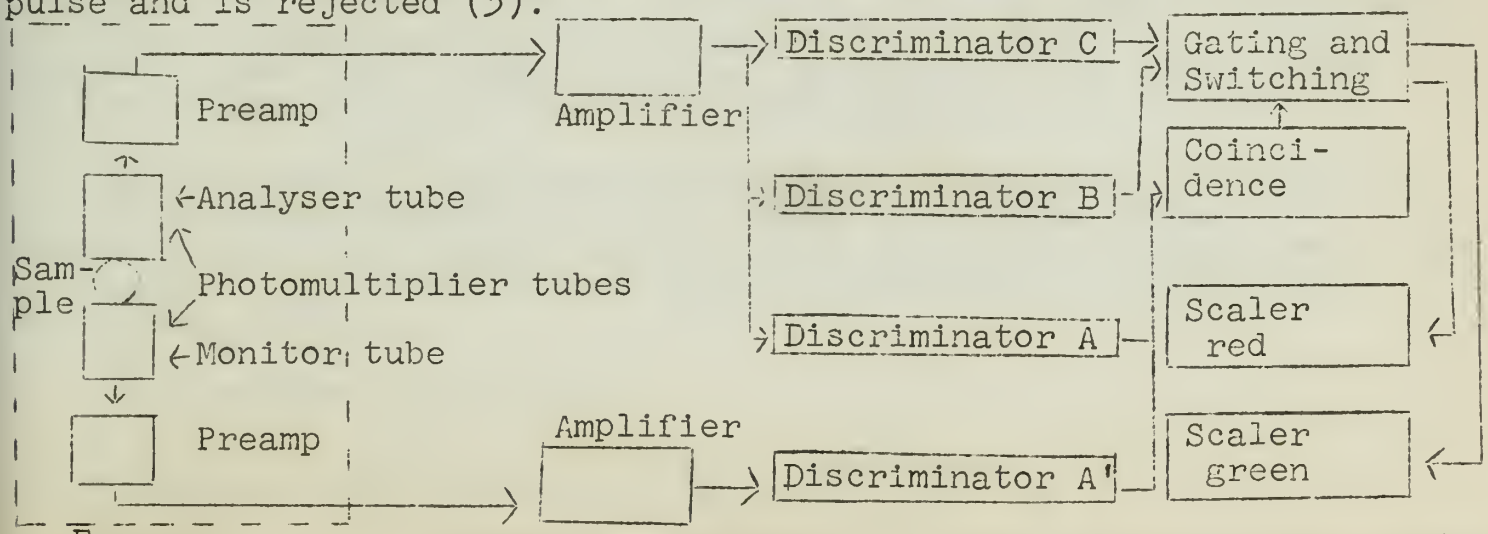
Reported by Rainer Berger November 14, 1957

A. Historic Background

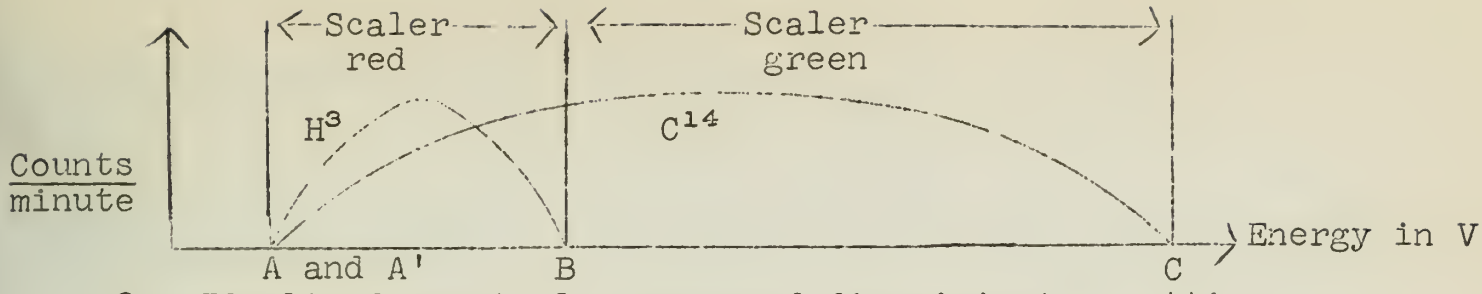
Liquid scintillation counting is based to a large extent on the fundamental research of H. Kallmann of New York University in 1947 on the method by which high energy radiation causes fluorescence (1). Further developmental studies were carried out mainly at the Los Alamos Scientific Laboratory (2).

B. Operating Principle

The idea of liquid scintillation counting is simply to dissolve the radioactive samplein a solution containing a fluorescent substance called a scintillator. Toluene is one of the best solvents and 2,5-diphenyloxazole an efficient scintillator. Radiation will cause the scintillator to emit light by an exponential process. This light is detected by the photosensitive layer of two photomultiplier tubes, the analyzer tube and the monitor tube. Assuming one photoelectron would cause the emission of 5 electrons at the first dynode and each electron again 5 secondary electrons, then the tube would operate with a multiplication factor of 5. If 11 dynodes were present, 5" electrons would have resulted. The output of each photomultiplier tube is amplified to about 0.1 volt in the preamplifiers and to 10 - 100 volts in the main amplifiers. Two channels of pulse height analysis, each provided with its own scaler, are obtained by three discriminators, A, B and C applied to the circuit from the analyzer tube. The monitor tube has only a single descriminator A' attached to its circuit. Discriminators A and A' are always equal and are varied by a single control. Output pulses from the discriminators A and A' are fed into a coincidence circuit. If they coincide in time, as from a scintillation in the sample, they are passed on to be counted. Pulses arriving at the coincidence circuit at slightly different times, as from random thermoionic pulses in the two photomultipliers, are rejected. Those pulses that do fire the coincidence circuit must be analyzed or sorted according to their height and recorded or rejected as desired. This is accomplished by the discriminators B and C. Should a pulse not exceed B, as with all tritium and some carbon-14 pulses in the simplified illustration 2, it is registered on the first scaler. It is registered on the second scaler if, as with most carbon-14 pulses, it exceeds B but not C. Anything beyond C can only be a background pulse and is rejected (3).



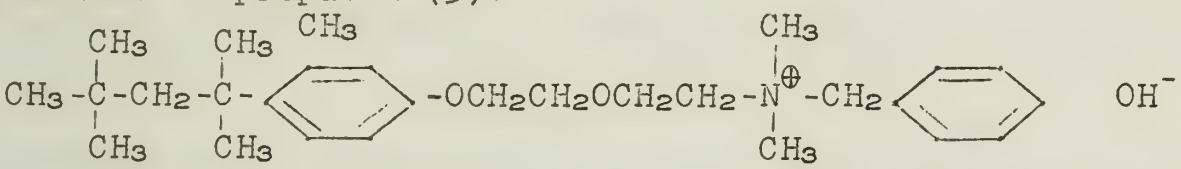
1. Simplified diagram of liquid scintillation counter.



2. Idealized spectral curves and discriminator settings.

C. Scintillation Counting Solvents

There are two classes of solvents: primary to comprise the bulk of the solution and secondary to assist in keeping a compound dissolved should it be insoluble in the primary solvent. The best primary solvents are the alkylbenzenes such as toluene and the xylene isomers along with 1,4 dioxane, ethylene glycol dimethylether and n-heptane which proved to be acceptable (4). In the category of secondary solvents fall methanol, naphthalene and Hyamine 10X, whose quarternary hydroxide is prepared (5).



p-diisobutyl cresoxy ethoxy ethyl dimethyl benzyl ammonium hydroxide from Rohm and Haas "Hyamine 10X" (6).

Many amino acids, hydroxyacids, proteins and carbon dioxide may be analysed by the quarternary hydroxide method.

It is interesting to note, that the transfer of the excitation energy from the solvent to the solute, the fluorescent scintillator, does not occur via an ionization process. Energy migrates from solvent molecule to solvent molecule until it reaches a solute molecule. In this process energy is transferred when distances are less than three atomic distances between the molecules (7).

D. Scintillation Counting Solutes

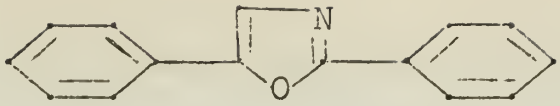
Primary as well as secondary solutes are in use. The function of the primary solute is to trap the excitation energy and emit it as photons along an exponential process. In order to obtain a more desireable spectrum of longer wavelength than the shorter of primary solutes, a secondary solute is employed in concentrations about a hundred times lower. More efficient matching of the light output to the photomultiplier sensitivity curve can thus be achieved (8).

Solutes should generally have a highly conjugated structure to yield an emission spectrum around 4000A, have a high degree of molecular symmetry free of steric strain and should contain no halogen, carboxyl or nitrosubstitution, which decrease the scintillation efficiency (9).

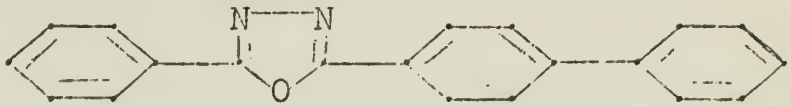
Good primary solutes are:

p-terphenyl 

2,4 diphenyloxazole (PPO)



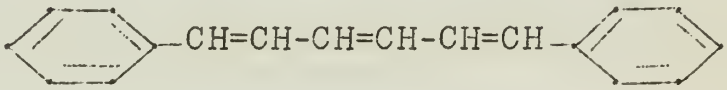
2-phenyl-5(4 biphenylyl)-1,3,4 oxadiazole (PDB)



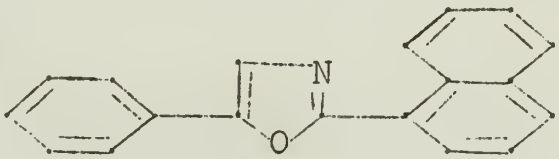
Good secondary solutes are:

1,4 Bis[5-phenyloxazolyl]benzene (POPOP)

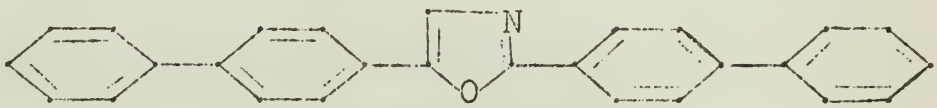
1,6 Diphenyl hexa-1,3,5-triene (DPH)



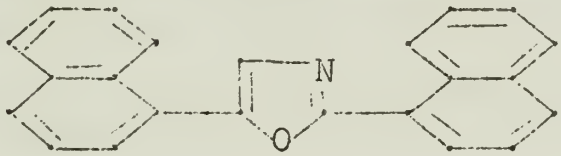
2 Naphthyl-5-phenyloxazole (NPO-

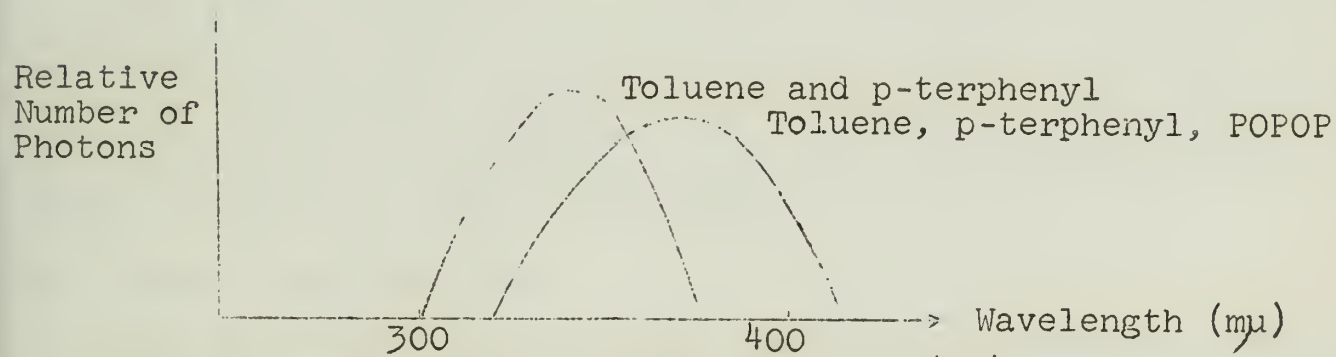


2,5 Bisbiphenyloxazole (BBO)



2,5 Dinaphthyloxazole





Shift of wavelength by secondary solute (10).

E. Quenching

The intensity of the light output is reduced by quenching, which has a number of origins.

Solvent quenching occurs when the excited solvent molecules do not transmit the energy to a fluorescent solute molecule, but lose it in the form of heat (7).

Solute quenching appears especially when the concentration of the solute becomes higher than about one millimole per liter. This self-quenching originates from the interaction between the solute molecules(7).

Furthermore the excited solute may lose the energy again to the solvent and also experience internal quenching in itself. A number of compounds are notorious quenchers, as acetaldehyde, acetone, acetic acid etc.

The following groups are arranged in order of decreasing quenching exhibited:

$$-CHO > -\overset{\overset{O}{\|}}{C}- > -OH > X > -C{\equiv}N > -\overset{\overset{O}{\|}}{C}-O- > -O- \quad (20).$$

Nitro compounds, peroxides, larger quantities of oxygen and colored compounds may be severe quenchers, so that it is better to combust the respective compounds to carbon dioxide and measure the radioactivity in an ion chamber with a vibrating reed electrometer.

F. Determination of Quenching

One of the methods to determine quenching is the Internal Standard Method (11). The correction factor obtained is of importance when comparing the radioactivities of compounds.

$$\text{Correction factor: } \frac{\text{Count of Internal Standard}}{\begin{matrix}(\text{Internal Standard})\\(\text{plus sample count})\end{matrix} - \text{sample count}}$$

If the correction factor is one, no quenching has occured. Any larger number signifies quenching.

G. Background

The total background is the sum of the effects of cosmic radiation, thermoionic emissions from the photomultipliers, ion and light feed back pulses and general electrical noise. In the interest of greatest possible suppression, shielding, refrigeration, light pipes and suitable electronics are employed. The Tri-Carb Instrument gives 5 dpm with quartz vials, whereas counting with low potassium content glass shows a higher rate due to some K^{40}.

H. Organic Applications

Generally speaking the scintillation counter should prove itself as an excellent tool in evaluating radioactive data from numerous investigations in organic chemistry as the study of

1. rearrangements
2. reaction paths
3. degradations
4. structure proof
5. stereochemical problems
6. catalytic reactions
7. functional group determination
8. loss or gain of carbon fragments
9. purity
10. analysis by isotope dilution assay
11. exchange reactions and
12. physical properties.

It would be too far reaching to attempt giving examples of all these possibilities, especially since for many nothing has been published so far, simply because the technique is still new and instruments are expensive.

In biochemistry so far one publication (22) mentions the use of a scintillation counter of the Tri-Carb series. Galactose-C^{14} and Sulfate-S^{35} were used in a metabolic study of brain functions. The lipids isolated were dissolved in toluene containing 0.3% 2,5 diphenyl oxazole as a scintillator and counted.

In organic chemistry (12) a determination of purity for allylamine-1-C^{14} has been carried out. By injecting a known amount of the compound into a Perkin-Elmer gas chromotography apparatus, first the position of the peak was checked against known pure inactive allylamine, secondly the fraction resembling just the peak was collected and analysed in the scintillation counter, which should contain all the activity and finally, the forerun and afterrun of the peak. These did not contain any activity. The specific activity of the allylamine had also been determined by counting a known amount in the scintillation instrument. Degradation of the active compound with ozone yielded formaldehyde, which was counted as the dimedon derivative dissolved in a 0.3% 2,5 diphenyloxazole-toluene scintillator solution.

$$\underset{(3)\ (2)(1)}{CH_2{=}CH\text{-}\overset{14}{C}H_2NH_2} \xrightarrow{O_3} \underset{(3)}{CH_2O} \longrightarrow \text{dimedon derivative}$$

No activity was found in the formaldehyde. All tests indicated the chemical and radio chemical purity among other determinations.

It has been difficult to count very labile or explosive organic compounds, either because they are hard to manipulate at ordinary temperatures or tend to explode in microcombustion set ups giving inaccurate results when determining the activity of the carbon dioxide. Now much compounds can be dissolved and counted at lower temperatures (12).

In paper chromatography it was often experienced that the eluents contained salts which after plating aliquots led to misleading results. Considerable absorption of radiation by the heavy atoms was the cause. The often tedious procedure of removing such salts does no longer have to be applied, when dissolving small amounts of the eluent in scintillation solutions (13).-- Exact knowledge of the fractionation efficiency of a column is often necessary, since it varies from column to column. A known amount of the radioactive counterpart of one of the inactive members of the mixture is placed into the still-pot. Once the fractionation functions, samples are removed from the still-pot, the distillate and of any other part of the column. After counting them, the efficiency may be determined, for the amount of radioactivity measured is directly proportional to the amount of the inactive counterpart present (12).

The determination of a radioactive compound is also made more convenient, when experiments necessitate the use of a Craig counter current apparatus. Distribution coefficients may be checked readily. 0.1 ml aliquots from each tube are assayed for activity. Then the distribution coefficient can be calculated from radioactive data (16).

Another use lies in the determination of equilibria between liquids and gases. The liquid phase may be counted immediately in the scintillation counter, whereas the gas is passed through an ion chamber connected to a vibrating reed electrometer, which with a steady value will indicate equilibrium conditions. The various amounts of activity are direct proportional to the liquid-vapor ratio (20).

Biochemists might be interested in rates of diffusion which can be easily found by counting the radioactive compound employed (14).

A very interesting feature of scintillation counting is multi-labeling (15). Compounds may be prepared containing different isotopes, whose combination depends on sufficiently different β-energies in order to be distinguished by the counter. Illustration 2 will assist in understanding. The following combinations are possible:

(C^{14} and H^3)-(C^{14} and P^{32})-(C^{14} and I^{131})-(C^{14} and Cl^{36})-(C^{14} and S^{35});
(H^3 and P^{32})-(H^3 and I^{131})-(H^3 and Cl^{36})-(H^3 and S^{35});
(H^3,C^{14} and P^{32})-(H^3, C^{14} and Cl^{36}) (H^3, C^{14} and S^{35})-(H^3, C^{14} and I^{131})

The most accurate way to determine the activity of two isotopes is the discriminator ratio method (15). The ratio of channel 2 cpm to channel 1 cpm is used. Both counts are obtained from standard samples of each of the isotopes. An equation is then derived that utilizes the discriminator ratio for each isotope instead of the counting efficiency as in other methods.

If N_1 = net cpm of channel 1, N_2 = net cpm of channel 2,
H_1 = net cpm of H^3 in channel 1, H_2 = net cpm of H^3 in channel 2,
C_1 = net cpm of C^{14} in channel 1, C_2=net cpm of C^{14} in channel 2,

$$a = \frac{H_2}{H}, \text{ and } b = \frac{C_2}{C_1} \text{ and}$$

$N_1=H_1+C$, also $N_2 = H_2+C_2$

then $H_1=\frac{bN_1-N_2}{b-a}$; H^3 dpm $= \frac{H_1}{\text{channel 1 } H^3 \text{ efficiency factor}}$.

Similarily $C_2 = \frac{b(N_2-aN_1)}{b-a}$

$$C^{14} \text{ dpm} = \frac{C_2}{\text{channel 2 } C^{14} \text{ efficiency factor}}.$$

I. Advantages of Scintillation Counting

(1) Sample preparation is easy and a large range of sample sizes from 5-80 ml is possible.
(2) No self-absorption and window absorption are experienced.
(3) Proportional response allows multi-labeling.
(4) Short dead time of counter permits high counting rates.
(5) Absolute calibration is simple.
(6) The sensitivity permits the determination of low levels of activity.

J. Preparation of Samples

Samples are counted in screw-cap bottles. If the compound is soluble in toluene, 13 ml of scintillator solution is placed into the screw-cap bottle. This solution contains for carbon-14 assay 3 g of diphenyloxazole (PPO) dissolved in one liter redistilled toluene. For tritium the solution contains 3 g of diphenyloxazole (PPO) per liter and 50 mg 1,3 Bis[5-phenyloxazolyl]benzene (POPOP) per liter in toluene. Small amounts of the compound are then added to make up the ready counting solution. After the count, a radioactive solution is added (i.e. 1 ml) which contains known radioactivity to determine any quenching.

Carbon dioxide may be counted by dissolving it in the quarternary hydroxide of hyamine 10X. The gas has been generated in a vacuum line or another closed system and is manipulated into a reaction tube containing a little more than the stoichiometric amount of the standardized quarternary hydroxide. The vessel is sealed off, time for reaction is allowed, and finally the contents of the tube quantitatively transferred with the above mentioned 2,5 diphenyloxazole-toluene solution to a screw-cap bottle and counted. About 40% efficiency is attained (17).

Materials insoluble in any primary solvent or solvent system containing a secondary solvent may be suspended in a thixcin gel, which is a castor oil derivative. The counting efficiency is reduced by about 10%. Thus it is possible to count $BaC^{14}O_3$, which does not have to be converted to carbon dioxide (18). Organic compounds like RDX, hexamine and the mercuric chloride of hexamine have already been applied to the suspension technique (19), which should open the way for the direct counting of insoluble organic derivatives (12).

Insoluble and highly colored materials are combusted on a vacuum line to be counted. Carbon-14 is converted to CO_2^{14} and H^3 to H_2^3O.

K. Absolute Sensitivity (20)

(Minimum amount of radioactivity which can be detected)
Conditions: 30 min. count to ± 10% accuracy with a 30 min. background count.

Isotope	Efficiency	Background c/m	Min. Isotope c/m	Min. Isotope μc
Tritium	25%	200	153	$6.9.10^{-5}$
C^{14} or S^{35}	75%	150	44	$2.0.10^{-5}$
El^{36}	85%	125	36	$1.6.10^{-5}$
P^{32}	95%	100	29	$1.3.10^{-5}$

Concentration Sensitivity
(Minimum concentration of radioactivity which can be detected in 40 ml of solution in 30 minutes with an accuracy of ± 10%)

	Isotope	dpm/ml	μc/ml
Scintillation Counter	H^3	7.1	10^{-6}
	C^{14}	1.5	10^{-6}
Windowless Geiger-Muller flow counter	H^3	554000	10^{-2}
	C^{14}	1480	10^{-4}
Ion chamber	H^3	60	10^{-5}
	C^{14}	60	10^{-5}

L. Counting times for a given standard error of net activity (21)

t_b = time in minutes for background count.

t_s = time in minutes for sample count.

Count sample / Count background	Error 1% t_b	1% t_s	5% t_b	5% t_s	10% t_b	10% t_s
1.1	68300	71700	2730	2870	683	717
2.0	804	1140	32	46	8	11
3.0	228	395	9	16	2	4
4.0	111	222	4	8	1	2
5.0	68	151	3	6	1	2
6.0	46	113	2	5	1	1
7.0	34	89	1	4	1	1
8.0	26	74	1	3	1	1
9.0	21	62	1	3	1	1
10.0	17	54	1	2	1	1

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Addendum:

A * represents papers presented at the Northwestern University Conference on Liquid Scintillation Counting, August 20 - 22, 1957, Evanston, Illinois.

CARBON ISOTOPE EFFECTS IN DECARBOXYLATION REACTIONS

Reported by A. H. Peterson November 18, 1957

This seminar will be concerned with the isotope effect observed in the decarboxylation of malonic and other acids on substitution of C^{13} or C^{14} in the carboxyl position. Various attempts to account theoretically for the experimentally observed results will be reviewed. A general review of thermal decarboxylation mechanisms has been made by Brown (1).

Malonic acid is decarboxylated readily by heating to moderate temperatures. If all of the carbon atoms present in a molecule of malonic acid are not the same isotope, the products of the decarboxylation reaction will be as follows, with the rate constants of their formation defined as shown (2).

$$H_2C(C^nOOH)(C^nOOH) \xrightarrow{k_1} C^nO_2 + C^nH_3C^nOOH \qquad 1$$

$$H_2C(C^xOOH)(C^nOOH) \xrightarrow{k_2} C^nO_2 + C^xH_3C^nOOH \qquad 2$$

$$C^xOOH \xrightarrow{k_3} C^xO_2 + C^nH_3C^nOOH \qquad 3$$

$$H_2C(C^nOOH)(C^nOOH) \xrightarrow{k_4} C^nO_2 + C^nH_3C^xOOH \qquad 4$$

Two types of isotope effect can be considered: intramolecular, in which the rates of breaking of C^{12}-C^{12} bonds and C^{12}-C^{13} or C^{12}-C^{14} bonds in the same molecule are compared, and intermolecular, which compares the rates of breaking of C-C bonds in molecules composed of a single isotope of carbon and in labeled molecules. The deviation of the ratio $\frac{k_4}{k_3}$ from unity is a measure of the intramolecular isotope effect, while various intermolecular isotope effects are measured by the deviation of $\frac{k_1}{2k_3}$, $\frac{k_1}{2k_4}$ and $\frac{k_2}{k_1}$ from unity (3).

Generally, effluent CO_2 is collected during the first few percent of reaction and the isotope ratio, $R=\frac{C^{13}O_2}{C^{12}O_2}$, of this sample as determined by mass spectrometer as compared with the isotope ratio of CO_2 obtained from combustion of malonic acid. The ratio $\frac{k_1}{k_3}$ is then determined from the relationship $\frac{\left(\frac{k_4}{k_3}\right)}{} = 2\left(\frac{R_D}{R_C}\right) - 1$, where R_C is the isotope ratio of the effluent CO_2 and R_D is the isotope ratio for total combustion. In the case of radioactive C^{14} isotopes, when the mole fraction of C^{14} in the label position is very small, the specific activity of the effluent CO_2, S_C, is compared with

the specific activity of the parent diacid, S_D. Then $\frac{(k_4)}{(k_3)} = \frac{(S_D)}{(S_C)} - 1$.

As a check on the results obtained by this method the product acetic acid may be oxidized to CO_2 and $\frac{k_4}{k_3}$ redetermined from this isotope ratio, R_A, or specific activity, S_A. Thus $\frac{k_4}{k_3} = \frac{(2\,R_A - R_D + R_A R_D)}{(3\,R_D - 2R_A + R_A R_D)}$ and $\frac{k_4}{k_3} = \frac{S_A}{S_D - S_A}$ (4).

Bigeleisen applied transition state theory to the effect of isotopic substitution on the rate of chemical reactions and obtained the following equation for the ratio of rate constants $\frac{k_4}{k_3}$ for a molecule of the type ABA' where A and A' are identical groups except for a difference in isotopic mass of one atom (5).

$$\frac{k_4}{k_3} = S \left(\frac{m_3^*}{m_4^*}\right)^{1/2} \left[1 + \sum_i^{3n-6} G(u_i)\,(u_{4i} - u_{3i}) - \sum_i^{3n'-6} G(u_i^{\ddagger})\,(u_{4i}^{\ddagger} - u_{3i}^{\ddagger}) \right]$$

In this equation k_3 and k_4 are the rate constants of reactions 3 and 4, S is the symmetry number, m* is the effective mass of the molecule in the transition state along the coordinate leading to products, 3n-6 is the number of vibrational modes of the molecule and G(u) is the free energy function defined and tabulated by Bigeleisen and Mayer (6). This function appears in the quantum mechanical expression for the equilibrium constant in isotope exchange reactions and has the form $G(u) = \frac{1}{2} - \frac{1}{u} + \frac{1}{e^u - 1}$ where $u_i = \frac{h\nu_i}{k\,T}$. Here h and k are the Planck and Boltzmann constants respectively, while ν_i is the frequency of vibration and T is the absolute temperature.

For this case where the isotopic groups A and A' are in the same molecule, the term $\sum_i^{3n-6} G(u_i)\,(u_{4i} - u_{3i})$ is equal to zero because the free energy of the unreacted molecule ABA' is the same whether reaction 3 or reaction 4 takes place. That is, $\sum_i^{3n-6} G(u_i)\,u_{4i} = \sum_i^{3n-6} G(u_i)\,u_{3i}$. This is equivalent to saying $u_{4i} - u_{3i} = 0$. Bigeleisen neglected the term $\sum_i^{3n-6} G(u_i^{\ddagger})(u_{4i}^{\ddagger} - u_{3i}^{\ddagger})$ which he thought would make only a negligible contribution. The effect of including these terms will be shown later. Elimination of these terms leaves the equation $\frac{k_4}{k_3} = S \left(\frac{m_3^*}{m_4^*}\right)^{1/2}$. Only the masses of the atoms between which the bond is broken influence the effective mass of the molecule in the transition state (7). Hence $\frac{m_3^*}{m_4^*}$ is equal to the reduced mass of the atoms separated in reaction 3 divided by the reduced mass of the atoms separated in reaction 4. For the C^{13} isotope effect

(n=12, x=13 and the symmetry number S=1 we find

$$\frac{k_4}{k_3} = \left(\frac{\frac{12 \times 13}{12 + 13}}{\frac{12 \times 12}{12 + 12}}\right)^{1/2} = 1.0198 \qquad (2)$$

and similarly for C^{14}, $\frac{k_4}{k_3}$ is equal to 1.038 (8). Note that these results are independent of temperature.

The experimental values found by various investigators for the $\frac{k_4}{k_3}$ ratio are listed in table I. The probable range of uncertainty was calculated in most of these cases by Yankwich and Stivers (4) from the published experimental results.

Table I

Intramolecular Isotope Effect in $CHR(COOH)_2$

R	x	State	T,°C	$\frac{k_4}{k_3}$	References
H	13	liquid	138	1.019 ± .001	2
H	13	liquid	138	1.026 ± .004	9
H	13	liquid	138-139	1.021 ± .001	9
H	13	liquid	160	1.033 ± .033	10
H	13	liquid	140	1.0292 ± .0007	11
H	13	liquid	138	1.026	12
H	13	liquid	137	1.028 ± .002	4
Br	13	liquid	137	1.024 ± .003	4
H	13	quinoline solution	140	1.0284 ± .0012	13
Theory Any	13		27-227	1.020	2
H	14	liquid	145	1.12 ± .03	14
H	14	liquid	153	1.06 ± .02	15
Br	14	liquid	122	1.41 ± .13	14
α-Naphthyl	14	liquid	163	1.076 ± .005	16
Phenyl	14	liquid	163	1.088 ± .016	16
α-Naphthyl	14	dioxane-aq.HCl	73	1.098 ± .012	16
α-Naphthyl	14	dioxane-aq.HCl	88	1.095 ± .008	16

Phenyl	14	dioxane-aq.HCl	73	1.132 ± .017	16
H	14	liquid	138	1.10	12
H	14	liquid	137	1.099 ± .005	4
Br	14	liquid	137	1.116 ± .004	4
Theory Any	14		27-227	1.038	8

Note that the simplified statistical mechanical treatment of Bigeleisen predicts a value of two for the ratio of C^{14} to C^{13} intramolecular isotope effects. While there is considerable variation in the values found by various investigators, it is apparent from table I that the ratio is much greater than two, probably at least three. The work of Yankwich and Stivers, for example, indicates a ratio of C^{14} to C^{13} effects of 3.6 ± 0.5 for malonic acid and 4.8 ± 0.9 for bromomalonic acid (4).

A similar effect was observed in the decarboxylation of mesitoic acid, where Stevens, Pepper and Lounsbury report a ratio of about 2.7 (17).

Since the observation of isotope effects depends upon the isotope ratio found in the first few percent of CO_2 liberated in the decarboxylation reaction, the data for experiments in the liquid state tend to give the value of the effect at the melting point regardless of the bath temperature. When the decarboxylation was carried out in quinoline solution over a temperature range from 90° to 130°C, a temperature dependence not predicted by Bigeleisen's equation was observed. The intramolecular isotope effect, $\frac{k_4}{k_3}$, decreased with increasing temperature (13). This indicates that in addition to the temperature independent factor which is fairly well approximated by Bigeleisen's equation there is a temperature dependent factor.

The rate of decarboxylation of malonic acid in dioxane solution is proportional to the concentration of amine (quinoline) added. This indicates that the reaction proceeds by association of the amine with either the hydroxyl group (hydrogen bonding) or with the carbon atom of the carboxyl group. The spectral data favoring the second possibility will be discussed later.

A rapid reversible equilibrium with solvent prior to the rate determining step would account for a deviation of the observed isotope effect in quinoline solution from that which would be observed in the absence of solvent (18). No calculation of the magnitude of this effect could be made from the data obtained for decomposition of the acid but values were obtained in the case of the mono-anion.

It has been shown that malonic acid exists in solutions of pyridine or quinoline in essentially undissociated form (19), while such strongly basic amines as N-ethylpiperidine neutralize one and only one carboxylic acid group. This allowed study of the effect of

quinoline on the decarboxylation of the mono-anion. Equilibrium constants may be defined for the solvation of the mono-anion by quinoline as follows (20):

$$^{\ominus}O_2CCH_2C^{12}O_2H + Q \underset{}{\overset{K_1}{\rightleftharpoons}} {}^{\ominus}O_2CCH_2C^{12}O_2HQ$$

$$^{\ominus}O_2CCH_2C^{13}O_2H + Q \underset{}{\overset{K_3}{\rightleftharpoons}} {}^{\ominus}O_2CCH_2C^{13}O_2HQ$$

Also there is the possibility of isotope discrimination in the formation of ionic species with C^{13} in a terminal position. K_x is defined as the equilibrium constant of this reaction.

$$\underset{(2\text{-}Z)}{HO_2C^{12}C^{12}H_2C^{13}O_2^{\ominus}} \rightleftharpoons \underset{(Z)}{{}^{\ominus}O_2C^{12}C^{12}H_2C^{13}OOH}$$

The relative concentrations of the two species are (2-Z) and (Z) respectively. Thus $K_x = \frac{(Z)}{(2\text{-}Z)}$. The effect of these equilibria on the isotope effect observed depends upon whether CO_2 is liberated from the carboxyl or carboxylate group (20). If the source is the carboxyl group,

$$H_2C^{12}\begin{cases} C^{12}OO^{\ominus} \\ C^{12}OOHQ \end{cases} \xrightarrow{\frac{k_1}{2}} \qquad K_1$$

$$H_2C^{12}\begin{cases} C^{12}OO^{\ominus} \\ C^{13}OOHQ \end{cases} \xrightarrow{k_3} \qquad (Z);\ K_3$$

$$H_2C^{12}\begin{cases} C^{13}OO^{\ominus} \\ C^{12}OOHQ \end{cases} \xrightarrow{k_4} \qquad (2\text{-}Z);\ K_1$$

then $\left(\frac{k_4}{k_3}\right)_{\text{obsd.}} = \left(\frac{k_4}{k_3}\right)\left(\frac{K_1}{K_3}\right)\left[\frac{(2\text{-}Z)}{(Z)}\right]$.

If carbon dioxide is liberated from the carboxylate group,

$$H_2C^{12}\begin{cases} C^{12}OO^{\ominus} \\ C^{12}OOHQ \end{cases} \xrightarrow{\frac{k_1}{2}} \qquad K_1$$

$$H_2C^{12}\begin{cases} C^{13}OO^{\ominus} \\ C^{12}OOHQ \end{cases} \xrightarrow{k_3} \qquad (2\text{-}Z);\ K_1$$

$$H_2C^{12}\begin{cases} C^{12}OO^{\ominus} \\ C^{13}OOHQ \end{cases} \xrightarrow{k_4} \qquad (Z);\ K_3$$

then $\left(\frac{k_4}{k_3}\right)_{\text{obsd.}} = \left(\frac{k_4}{k_3}\right)\left(\frac{K_3}{K_1}\right)\left[\frac{(Z)}{(2\text{-}Z)}\right]$.

Expressions may be similarly obtained for the intermolecular effect $\frac{k_1}{2k_3}$ also in terms of K_x and $\frac{K_1}{K_3}$. By solving the two pairs of simultaneous equations, Yankwich and Weber obtained the values listed in table II for $\frac{K_1}{K_3}$ and K_x.

Table II

Temperature, °C	127		91	
Source	K_x	$\frac{K_1}{K_3}$	K_x	$\frac{K_1}{K_3}$
CO_2H	1.0076 ± .0020	1.0063 ± .0013	1.0084 ± .0020	1.0069 ± .0013
CO_2^-	1.0050 ± .0016	1.0063 ± .0017	1.0054 ± .0016	1.0069 ± .0017

Yankwich and Weber had hoped to show by this work which group, carboxyl or carboxylate, was the source of the CO_2 liberated. The relative values of $\frac{K_1}{K_3}$ and K_x can be estimated by comparison of the expressions for these quantities in terms of the partition functions, f, from which all common terms have been removed.

$$\frac{K_1}{K_3} = \frac{[^-O_2CCH_2C^{12}O_2HQ]}{[^-O_2CCH_2C^{12}O_2H][Q]} \cdot \frac{[^-O_2CCH_2C^{13}O_2H][Q]}{[^-O_2CCH_2C^{13}O_2HQ]}$$

$$\frac{K_1}{K_3} = \frac{f C^{12}O_2HQ \cdot f C^{13}O_2H}{f C^{12}O_2H \cdot f C^{13}O_2HQ} = \frac{f C^{13}O_2H / f C^{12}O_2H}{f C^{13}O_2HQ / f C^{12}O_2HQ}$$

$$K_x = \frac{[^-O_2C^{12}C^{12}H_2C^{13}O_2H]}{[HO_2C^{12}C^{12}H_2C^{13}O_2^-]}$$

Here the partition function of each ion is approximated by the product of the partition functions of the carboxyl and carboxylate groups.

$$K_x = \frac{f C^{12}O_2^{\ominus} \cdot f C^{13}O_2H}{f C^{12}O_2H \cdot f C^{13}O_2^{\ominus}} = \frac{f C^{13}O_2H / f C^{12}O_2H}{f C^{13}O_2^{\ominus} / f C^{12}O_2^{\ominus}}$$

The hydrogen bonded molecule formed by association of quinoline may be regarded as having partially lost its hydrogen ion while the mono-anion is the limiting case in which the hydrogen ion is completely removed. Thus the deviation from unity of the denominators in the last expressions for $\frac{K_1}{K_3}$ and for K_x have the same sign. Consideration of the reduction in frequency of the C=O and C-O bonds on formation of an anion from an acid indicates that the ratio $f C^{13}O_2^{\ominus} / f C^{12}O_2^{\ominus}$ is probably smaller than $f C^{13}O_2HQ / f C^{12}O_2HQ$. Consequently, the deviations of K_x and $\frac{K_1}{K_3}$ from unity should have the same sign and that of K_x should be greater. While these conditions are fulfilled by the values obtained for the carboxyl group as a source, the experimental errors are too large to eliminate the carboxylate group as a source (20).

The previously mentioned asscciation of the amine quinoline with the carboxyl carbon of malonic acid (neglected in the preceding discussion) results in a shift in the carboxyl band near 1720 cm^{-1}. Addition of the base N-butylpiperidine (NBP) results in a drastic reduction in the intensity of this band and the formation of the

characteristic carboxylate band near 1600 cm^{-1} and another broad band about 1485 cm^{-1}. Table III shows the shift of the carbonyl band and the apparent rate constants observed in various media (3).

Table III

Solvent	Carbonyl Frequency, cm^{-1}	Apparent rate const. at 99.6°; k x 10^4, sec^{-1}
Quinoline (Q)	1705	4.6
Quinoline + NBP	1715	2.7
Dioxane (D)	1732	0.066
Dioxane + NBP	1727	2.10
0.27M Q in D	--	0.28
0.35M Q in D	--	0.43
1.59 Q in D	1715	1.18
4.24M Q in D	1710	2.95
Quinoline (extrapolated)	--	(6.0)

The shift in the carbonyl band reported was due to the reduction of intensity of the unsolvated band at 1732 cm^{-1} and appearance of the soluated band at 1705 cm^{-1} on the addition of quinoline to a dioxane solution of malonic acid. The two bands were not resolved but appeared as a single broad band whose center was at the position reported.

The 10 cm^{-1} increase in the carbonyl band on addition of NBP to quinoline solutions of the diacid is probably due to the combination of two effects - a decrease of about 5 cm^{-1} due to formation of the mono-anion as observed when NBP is added to the diacid in dioxane, and an increase of 15 cm^{-1} due to weakening of the carboxyl solvation by quinoline (3).

While the rate of decarboxylation of malonic acid in quinoline-dioxane solution is first order in dependence on quinoline concentration, no evidence has been found for similar catalysis of anion decomposition. Quinoline acts as both solvent and specific catalyst for the free acid. A comparison of the rate in pure quinoline with the extrapolated rate from quinoline-dioxane mixtures (table III) indicates that the general (solvent) influence of quinoline decreases the rate although this carboxyl solvation of the free acid is apparently a prerequisite to the specific catalytic activity of quinoline (3).

Although the model of Bigeleisen was shown to correspond quite well to the observed isotope effects of C^{13}, because the results with C^{14} did not agree, Pitzer proposed a different model based on the

vibrations of the carboxyl group (this was neglected in Bigeleisen's three center model) for the transition state. In this model,

R and OH were considered to vibrate as single particles; the effective mass of each was assumed to be 16 in order to simplify calculations. The frequencies of vibration of the "heavy" molecule containing C^{14} were calculated from the force constants required to produce the observed frequencies in the normal acid, by substituting 14 for 12 as the mass of the carboxyl carbon. The frequencies of the transition state were calculated with the aid of the following assumptions: the force constants of the C=O and C-O bonds remain the same as in the unreacted acid and the force constant of the R-C bond which is broken is zero. The bending constants were set equal to zero and all other frequencies omitted by the model were assumed to be the same as in the normal molecule. Thus only the C=O and C-O vibrations of the transition state need to be considered. The observed frequencies of the C^{12} acid and the calculated frequencies for the C^{14} acid and for the transition states obtained from each acid are listed in terms of their wave numbers (ω, cm^{-1}) in table IV (21).

Table IV

$\omega(C^{12})$	$\omega(C^{14})$	$\Delta\omega$	G(u)	G(u)Δu
	Normal Acid	Molecule		
1800	1713	87	0.343	0.107
837	834	3	0.219	0.002
493	490	3	0.140	0.002
1423	1346	77	0.301	0.083
483	481	2	0.138	0.001
700	659	41	0.180	0.029
				$\sum$ = 0.222
	Transition State			
1711	1633	78	0.332	0.093
1088	1053	35	0.260	0.032
				$\sum$ = 0.125

The last column of table IV lists the G(u)Δu terms which were neglected by Bigeleisen in his earlier calculation of $\frac{k_4}{k_3}$. The equation for $\frac{k_4}{k_3}$ derived by Bigeleisen (5) as applied to this model

has the form:

$$\frac{k_4}{k_3} = \left(\frac{m_3^*}{m_4^*}\right)^{1/2} \left[1 + \sum_i^{3N-6} G(u_i)\, \triangle u_i - \sum_i^{3N-7} G(u_i^{\ddagger})\, \triangle u_i^{\ddagger}\right]$$

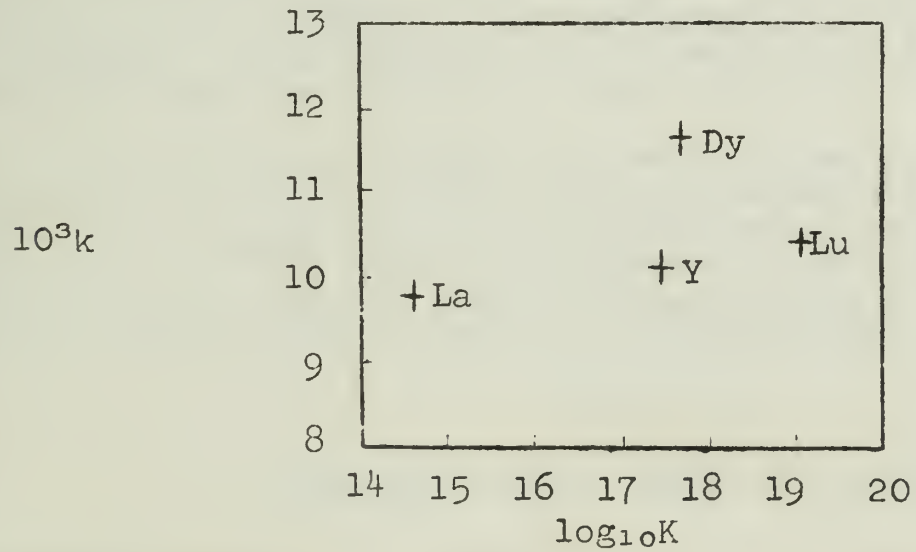
$$= 1.04 \quad [1 + 0.222 - 0.125] = 1.137$$

This calculation has not been repeated for the C^{13} isotope effect.

This calculated value of 1.137 for the intramolecular C^{14}-isotope effect is not, however, in good agreement with the more recent experimental results.

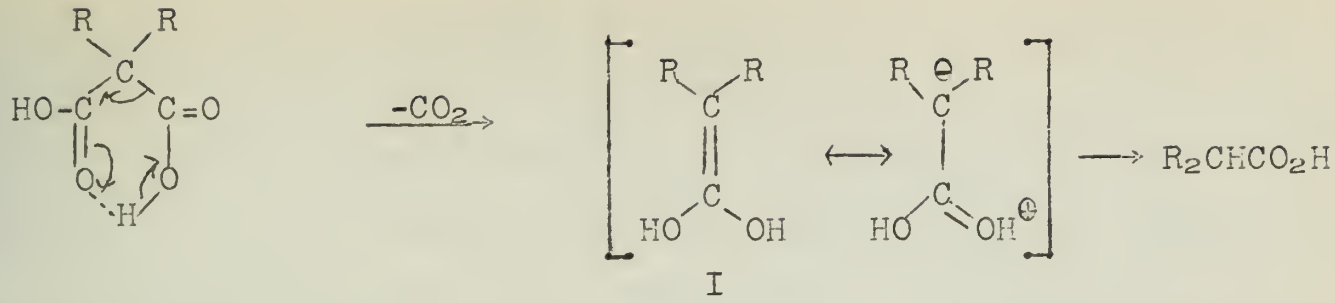
Although the validity of the experimental evidence indicating that the C^{14} isotope effect is some three times greater than the C^{13} isotope effect has been questioned (22), this unusual effect is apparently real. Pitzer and Gelles have suggested as a possible cause of this effect the non-zero nuclear spin and magnetic moment of C^{13} (23).

The rate of decarboxylation of phenylmalonic acid was studied in the presence and absence (24) of rare earth ions. The effect of the rare earth ions on the rate of the reaction due to changes in the ionic strength of the solution should be a smooth function of their ionic radii. The order of decreasing radii is La^{3+}, Dy^{3+}, Y^{3+}, Lu^{3+}. When the rate constant for the decarboxylation in the presence of each of these ions at a concentration of 0.48 M is plotted against the logarithms of the equilibrium constants of these ions with ethylenediaminetetraacetic acid (a measure of the chemical activity of the ion), the following chart results (25).



The acceleration by Dy^{3+} is apparently connected with the unpaired 4*f* electrons which cause it to be paramagnetic. The three other ions are diamagnetic.

One possible mechanism may be formulated as follows:



I

In malonic acids the two R groups are normally in a plane perpendicular to the plane of the C-C-C skeleton. Consequently, unless the carbon atom bearing the two R groups rotates during the decarboxylation the double bond in structure I is twisted 90° into the position required for cis-trans isomerization (25). While decarboxylation would not occur by a singlet mechanism unless this rotation takes place, the reaction could occur by excitation to a triplet state, the energy of which is not affected by rotation of the bonded atoms.

It had previously been postulated that cis-trans isomerizations may occur by means of such a nonadiabatic reaction involving a transition from a singlet to an excited triplet state as well as by an adiabatic reaction having a higher activation energy (26). Eyring and Harman (27) suggested that the probability of transitions from singlet to triplet states would be increased by paramagnetic ions. The non-homogenous magnetic field provided by the paramagnetic ions would act differently on the two magnetic dipoles arising from the spin of the two electrons in the π-bond.

Since phenylmalonic acid did not seem to bind the rare earth ion as strongly as was desired, the investigation was shifted to oxaloacetic acid. With this acid an increase in the rate of decarboxylation was observed with the paramagnetic Gd^{3+} and Dy^{3+} ions as compared to the effect of the diamagnetic ions La^{3+}, Y^{3+} and Lu^{3+}. For example, the catalysis by Dy^{3+} was some 20% greater than by the otherwise very similar Y^{3+} ion (28, 29).

The C^{13}-isotope effect in the decarboxylation of natural oxaloacetic acid in aqueous solution was measured alone and in the presence of diamagnetic yttrium and paramagnetic dysprosium ions. The $C^{13}O_2$ to $C^{12}O_2$ ratio was measured at 5%, 10% and 100% reaction, and the rate constants for the decarboxylation calculated. The intramolecular isotope effect is shown in table V.

Table V

	Oxaloacetic Acid (pH=1)	Y^{3+} oxaloacetate	Dy^{3+} oxaloacetate
$100\left(\frac{k_{12-12}}{k_{12-13}}-1\right)$	6	5 ± 1	10 ± 1

Thus it will be noticed that Y^{3+} ions had no significant effect on the isotope effect while the paramagnetic Dy^{3+} ion caused a significant change. The rate of fission of C^{12}-C^{12} bonds was increased about 4% more by the unpaired 4f electrons of Dy^{3+} than the fission of C^{12}-C^{13} bonds. This may be interpreted as an

indication that C^{13} nuclear spin-electron spin interactions are of the same order of magnitude as the electron spin-electron spin interactions produced by the paramagnetic ion at a greater distance from the electrons of the bond. In a C^{12}-C^{13} bond the C^{13} nuclear spin effect is already operating on the spins of the electrons of the π-bond; consequently, the effect of paramagnetic ions will be greater on C^{12}-C^{12} bonds where this effect is not yet present (30).

It should be noted that if the above theory is correct the model of Bigeleisen must be in error. Since both C^{12} and C^{14} have zero nuclear spin, a model neglecting the effect of nuclear spin on the rate of bond fission should produce agreement with experimental results for these two isotopes but not for C^{13} with its non-zero nuclear spin. Since Bigeleisen's model agreed much more closely with experimental results for C^{13} than for C^{14} these two theories are clearly at odds. The problem may be cleared up when work promised by Gelles and Reed on the effect of paramagnetic ions on the C^{14}-isotope effect is published.

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STABLE PHENOXY RADICALS

Reported by R. W. Bush November 21, 1957

INTRODUCTION

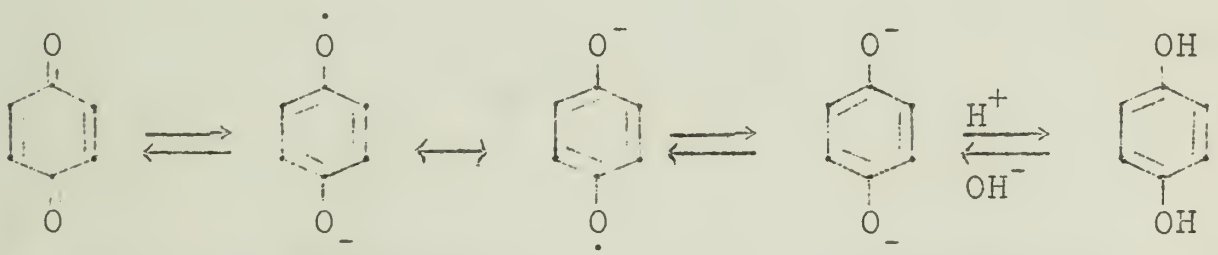
The formation of unstable organic oxygen radicals by decomposition of peroxides is a well-documented process and has been discussed in part in a recent seminar (1). Another group of organic oxygen radicals is the phenoxy radicals, prepared by oxidation of phenols. Recent work in the preparation, structure, and reactions of stable phenoxy radicals is the main topic of this seminar. Because of the structural similarities, semiquinones will also be discussed briefly.

The essential stabilizing factor in both the phenoxy radicals and the semiquinones is the aromatic nucleus, which allows delocalization of the free electron by formation of quinoid resonance structures. Thus, although these compounds are designated as "oxygen" radicals, carbon atoms throughout the molecule share the unpaired electron with the oxygen.

Stable oxygen radicals not containing a direct oxygen-aromatic nucleus bond, e.g. organic nitric oxides (R_2NO) and the metal ketyls ($R_2CO^-M^+$), are not discussed here.

I. SEMIQUINONES*

Semiquinones are intermediates in the reversible conversion of quinones to hydroquinones. They exist only when the conversion is carried out in basic solution, for this allows formulation of symmetrical resonance impossible in neutral or dilute acid solution (2):



quinone semiquinone hydroquinone

In concentrated acid, a di-protonated form of the semiquinone might be expected to occur, again allowing symmetrical resonance structures. Whether such stable semiquinones occur in concentrated acid has not been demonstrated. Other, less important resonance structures contributing to the stability of the semiquinones in basic solution are of the form:

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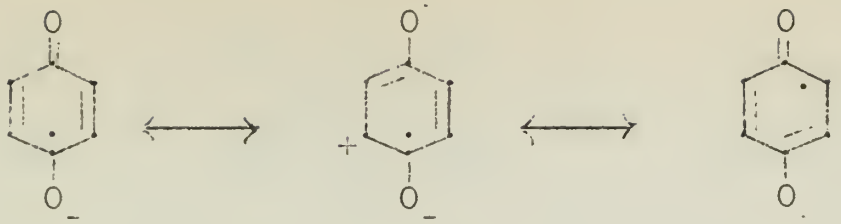
*This treatment of semiquinones is not exhaustive, but serves mainly as an introduction to the less-thoroughly-investigated phenoxy radicals.

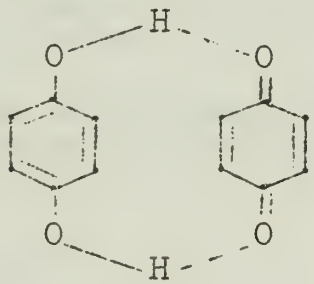


Similar, but less stable semiquinones would be expected as derivatives of ortho-quinones.

Semiquinones are prepared by three general methods: oxidation of hydroquinones, reduction of quinones, or by mixing equivalent amounts of the two (3). To delay the second step of the reduction of quinones to hydroquinones, mild reducing agents such as glucose or sodium hydrosulfite are preferred.

Potentiometric studies as well as detection of paramagnetism by magnetic susceptibility measurements originally established the existence of the semiquinones as free radical intermediates. In the reduction of 9,10-phenanthraquinone-3-sulfonate, the experiments showed that in very dilute solution the intermediate consisted of nearly 100% free radical (4). At higher concentrations and in acid solution the intermediate tended to dimerize.

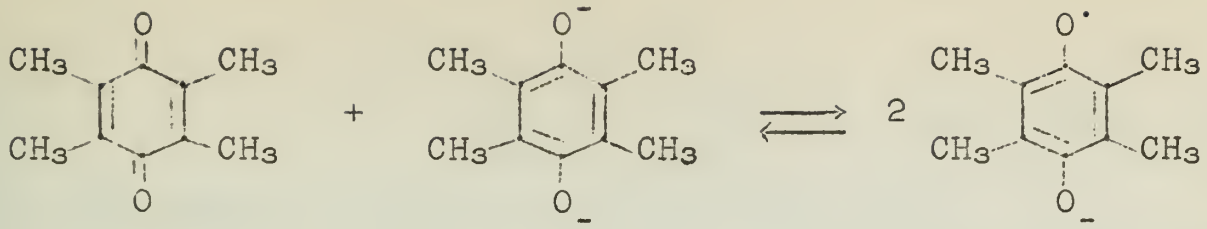
Because of rapid decomposition of benzoquinone in basic solution the existence of benzosemiquinone was not established (5). In acid solution, diamagnetic crystals of a dimer could be isolated as a stable intermediate in the reduction of benzoquinone. This quinhydrone has been formulated as follows (6,7):



To permit correct bond distances and angles the planes of the rings must be parallel.

Similar experiments on the duroquinone system showed a free radical intermediate which did not dimerize, even in acid solution (5). It was suggested that the eight methyl groups interfered to prevent the parallel ring orientation required for the dimer. By a different method, preparation of duroquinhydrone crystals was achieved, but the compound was highly unstable as expected and dissociated rapidly in solution (8).

The stability of durosemiquinone was clearly shown in an equilibrium reaction with non-radical species (9). The combination of equal parts of duroquinone and durohydroquinone in basic solution resulted in the formation of a deep yellow solution of durosemiquinone:



By absorption measurements at 440 mμ, the equilibrium constant for the reaction as written was found to be 1.28, independent of temperature from 15° to 30°C.

Thus two major reactions of semiquinones leading to non-radical species are dimerization and disproportionation. Stability of a semiquinone is therefore afforded by steric hindrance, preventing dimerization, and by resonance, preferentially stabilizing the radical (2).

Recently the newly developing technique of electron spin resonance measurement (ESR) has become a powerful tool in the investigation of paramagnetic compounds (10,11,12). As a device for elucidating the nature of semiquinones, ESR not only can detect the existence of a free electron with far greater sensitivity than can magnetic susceptibility measurements, but ESR hyperfine structure has given some clues about delocalization of the free electron. Thus, in the ESR spectrum of durosemiquinone there exist 13 hyperfine splitting lines, corresponding to interaction of the free electron spin with the spins of the 12 methyl protons (10):

$$\text{number of hyperfine lines} = 2nI + 1$$

n = number of equivalent protons
I = proton nuclear spin = 1/2

The hyperfine structure of durosemiquinone gives direct evidence for hyperconjugation of the methyl hydrogens (3,13).

Recent ESR investigations of other semiquinones are given in references 10, 11, and 12. Even benzosemiquinone, obtained in very low concentration, was detected by ESR (3,14).

II. PHENOXY RADICALS

The early work of Goldschmidt (15) and of Pummerer (16) on oxidation of phenols initiated the hunt for phenoxy radicals of more than transient stability. Stable radicals claimed by Goldschmidt to be of the form

R = OCH_3, OC_2H_5, Cl

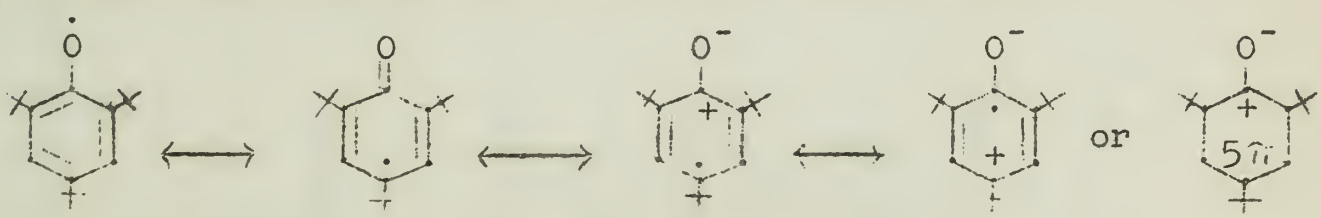
have been shown to exist as a radical only upon irradiation (17). Evidence for the existence of a stable anthroxy radical has also been reported (18). Within the past five years a number of stable phenoxy radicals have been prepared, some of which have even been isolated as crystals. (See table on page 196.) Stable phenoxy radicals are characterized by para- and ortho-groups which contribute to stability by steric effect, by resonance, and/or by inertness to dehydrogenation.

In general the phenoxy radicals have been prepared by oxidation of the corresponding phenol with lead dioxide, or better with alkaline potassium ferricyanide (19). Reactions were carried out in inert solvents (e.g. benzene, ether, carbon tetrachloride) under an atmosphere of nitrogen. Most phenoxy radicals react rapidly with oxygen to form peroxides. Quantitative estimation of the radical is made by determination of I_2 liberated from excess sodium iodide. If, however, the radical exists in equilibrium with a dimer, oxidation of iodide cannot determine the net radical content. Magnetic susceptibility measurements and colorimetry have been used to determine the position of the equilibrium.

A. Trialkylphenoxy Radicals

The most stable of the trialkylphenoxy radicals is 2,4,6-tri-t-butylphenoxy (20), prepared in 99-100% yield in solution by oxidation of a benzene solution of the phenol with alkaline ferricyanide (21). Concentration of the solution affords dark blue crystals having magnetic susceptibility corresponding to 70-85% free radical (22). The crystals are surprisingly stable; when stored under nitrogen their half-life is 7 days (23). ESR studies have confirmed the radical nature of tri-t-butylphenoxy (22,24).

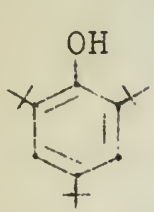
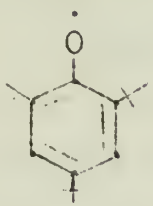
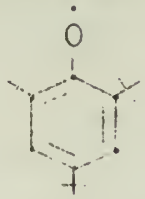
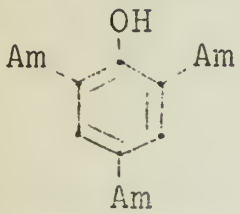
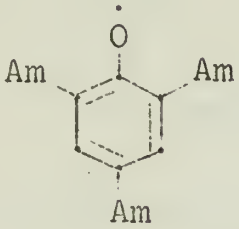
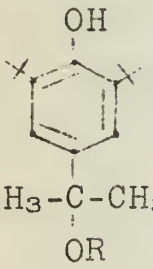
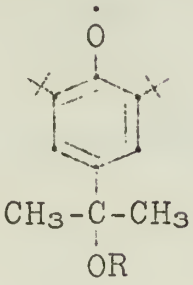
The following resonance structures have been suggested as important contributors to the stability of the radical:

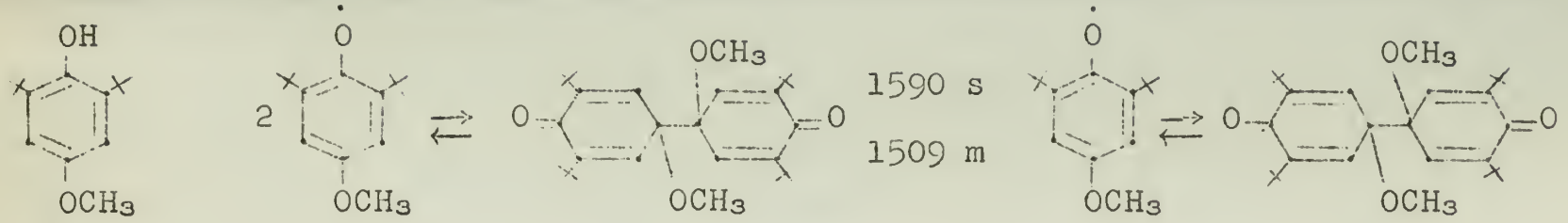


Ti = $C(CH_3)_3$

The reactivity of the compound at positions other than the phenoxy oxygen in typically free radical reactions suggests extensive delocalization of the electron. In the infrared spectrum, a very strong band occurs at 1573 $cm.^{-1}$ and has been found characteristic of most of the other phenoxy radicals. The position of this band in the region of carboxylate stretching suggests that it may correspond to the phenoxy C-O bond.

Stable Phenoxy Radicals

Phenol	Phenoxy in Solution	IR max cm.$^{-1}$	Phenoxy as Solid	IR max. cm.$^{-1}$	Ref.
		1573 s 1507 m			19 21 22 23
+ = t-butyl	dark blue		dark blue crystals m. 98-100°		
		1573 s 1507 m			28
Am = t-amyl	dark blue				
					28 31
R = CH_3, C_2H_5	dark blue				

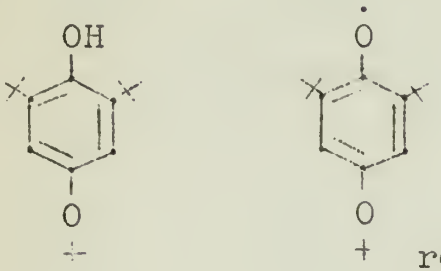


1590 s
1509 m

1655 s
1590 s
(pure sample)

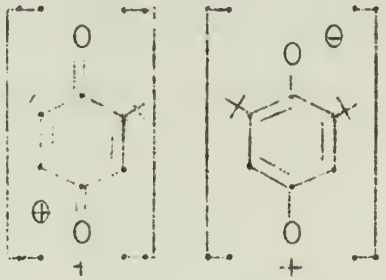
red-black oil

28
32



red-violet

1590 s
1509 m



colorless crystals
m. 88-92°C

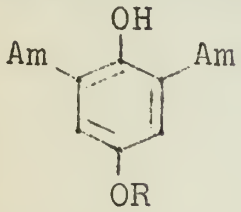
1630)
1650) s
(KBr)

28
25

red

1590 s
1509 m

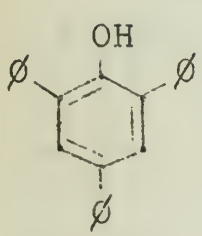
28



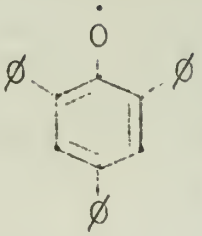
R = CH_3, Am

red

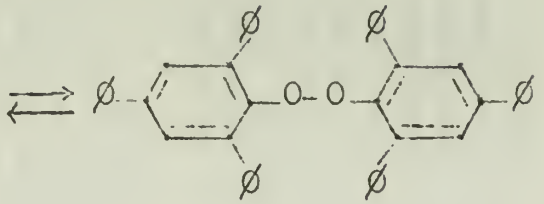
28

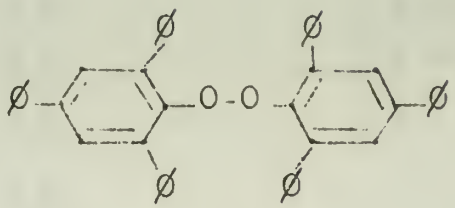


Ø = C_6H_5



red

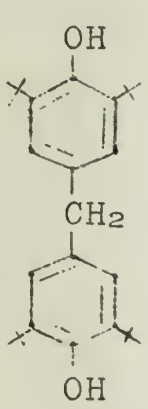


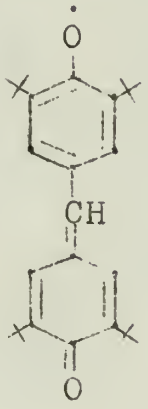


colorless crystals
m. 142-160°C

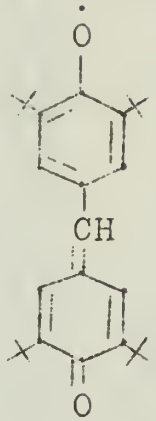
1670 s
1645 m
1515 s
(KBr)

35





dark blue

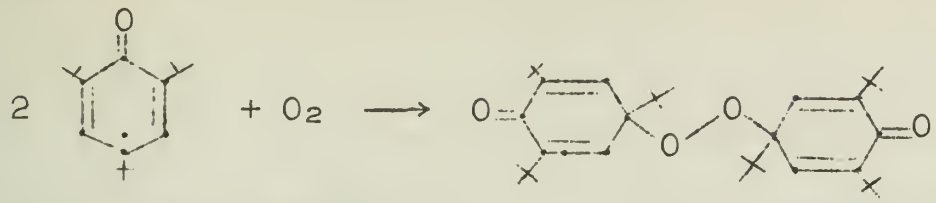


dark blue crystals
m. 153-158°C

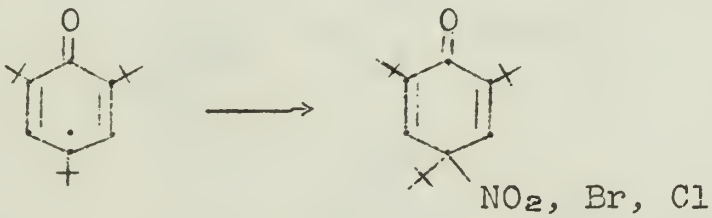
1572 s
(KBr)

36
37

Tri-t-butylphenoxy rapidly forms a peroxide by reaction with molecular oxygen:



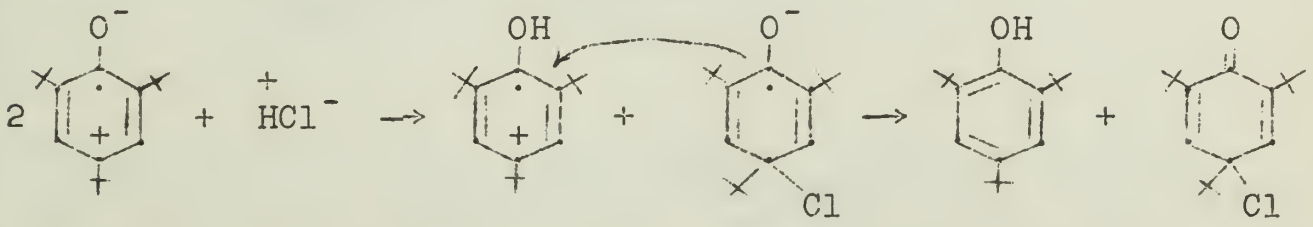
Proof of the structure of the peroxide is afforded in part by its thermal decomposition into 2,6-di-t-butylquinone, 4-t-butoxy-2,6-di-t-butylphenol and isobutylene (25,26). Similar para attack is effected by nitrogen dioxide, by bromine, and by iodobenzene dichloride, $C_6H_5ICl_2$ (21,22):



No ortho substituted products were reported. The reaction can be reversed with regeneration of the phenoxy radical by treatment of the cyclohexadienone with a metal, especially silver (23), or with sodium iodide. Since the cyclohexadienone halides can be prepared by direct halogenation of the phenol, this reaction provides a second route to the phenoxy radical.

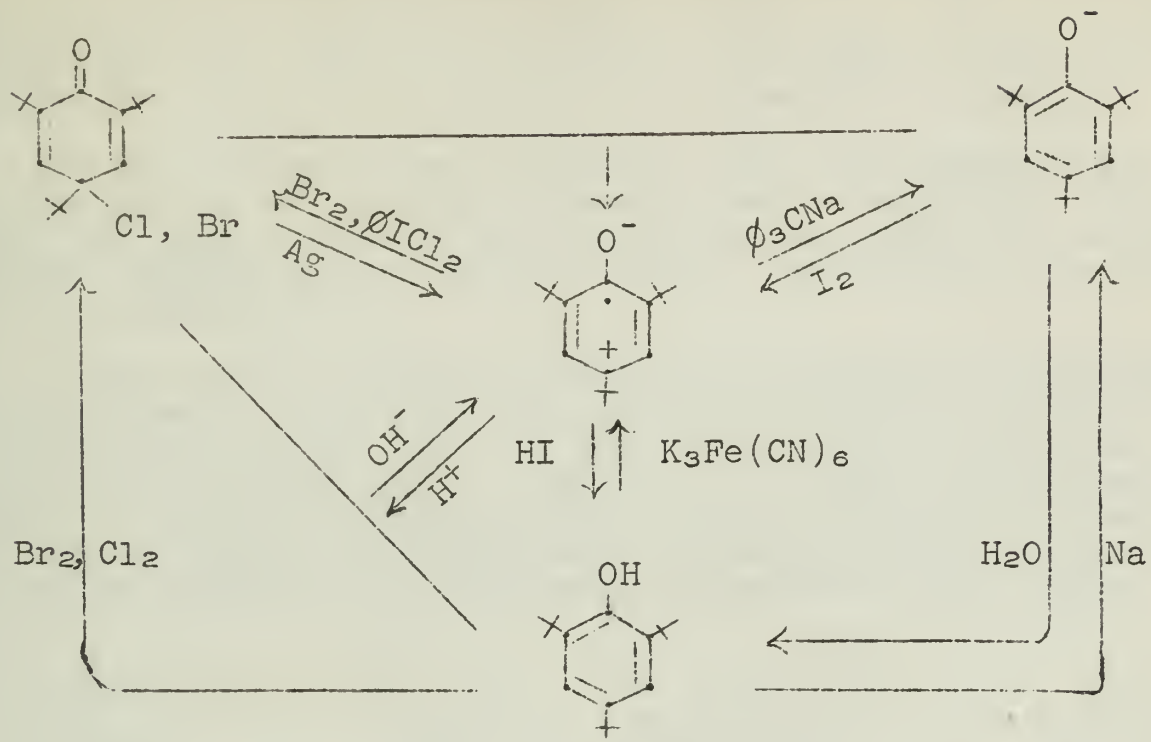
The usefulness of tri-t-butylphenoxy as a dehydrogenating agent depends upon reactivity at its oxygen atom. Most phenolic compounds, for example, phenol and hydroquinone, are rapidly dehydrogenated, with accompanying formation of tri-t-butylphenol. Similarly, elemental sodium, triphenylmethylsodium and phenyllithium attack the phenoxy oxygen, forming metal tri-t-butylphenoxides. The phenoxy radical may be re-formed by treatment of the phenoxide with iodine. Therefore, iodine treatment of sodium phenoxide prepared directly by reaction of the phenol with sodium affords a third method of preparing tri-t-butylphenoxy.

Reaction of the phenoxy radical occurs at the para carbon or at the oxygen, apparently depending primarily upon the stability of the product formed. In reaction with concentrated aqueous hydrochloric acid, attack occurs at both positions, followed by a postulated electron transfer (27):



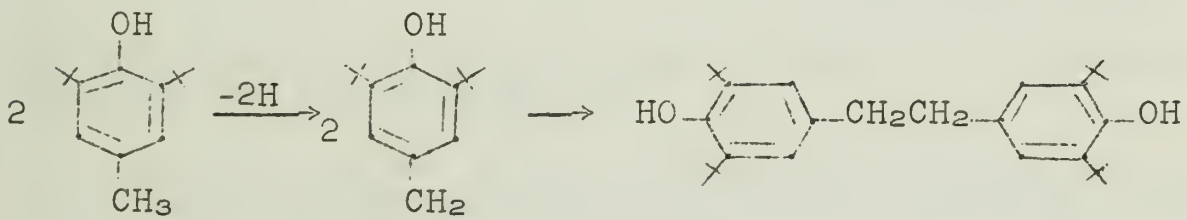
There is, however, no conclusive evidence for this mechanism. The same products were obtained with anhydrous hydrogen chloride in benzene solution. Under alkaline conditions the reverse reaction, a "comproportionation" can be made to occur.

The interconvertibility of tri-t-butylphenoxy and its derivatives is summarized in the following diagram:



Tri-t-amylphenoxy has been prepared in solution and found to be somewhat less stable than tri-t-butylphenoxy (28).

Benzylic or α-hydrogens on the phenol substituents prevent formation of stable free radicals. The oxidation of 4-methyl-2,6-di-t-butylphenol affords a dibenzyl dimer, doubtless formed via a benzyl radical intermediate (29):



a b c

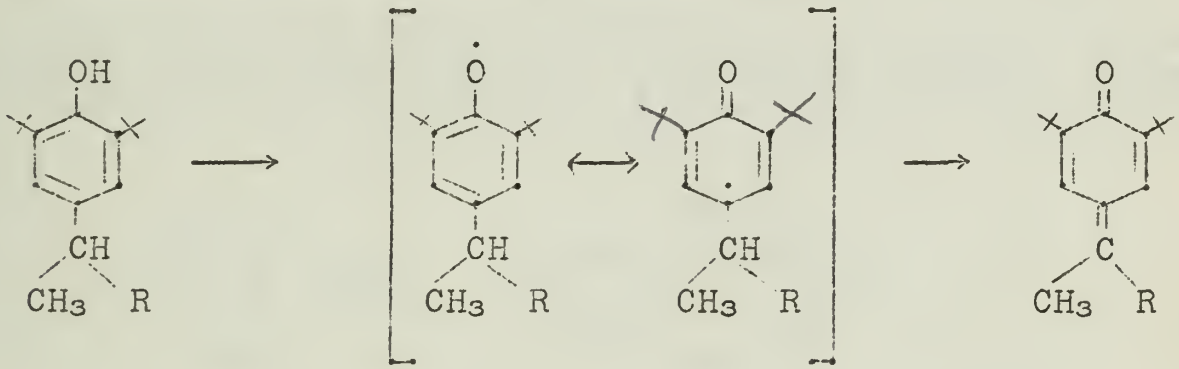
d

Evidence has been found suggesting the initial formation of a phenoxy radical, which rapidly rearranges to the benzyl radical (30). Since the products of the oxidation of the phenol give no evidence for intermediate phenoxy formation, the preparation of the phenoxy radical was attempted by a different route. Bromination of 4-methyl-2,6-di-t-butylphenol yielded 4-bromo-4-methyl-2,6-di-t-butyl-2,5-cyclohexadienone. Treatment of this cyclohexadienone with sodium iodide was expected to involve formation of the phenoxy radical. The main product was the dimer c above, along with some d

and an equivalent amount of the original phenol. The equivalent amounts of compound d and the phenol imply that dehydrogenation of c was accomplished by the phenoxy radical. This rearrangement of the phenoxy radical to benzyl radical suggests that the phenoxy radical may also occur in the direct oxidation of the phenol. The radical is observed transiently as a deep blue solution.

On the basis of this reaction, Cook (30) suggests two requirements for occurrence of stable phenoxy radicals. First, the ortho and para positions must have substituents bulky enough to prevent nuclear dimerization. Second, there must be no α-hydrogens on these substituents.

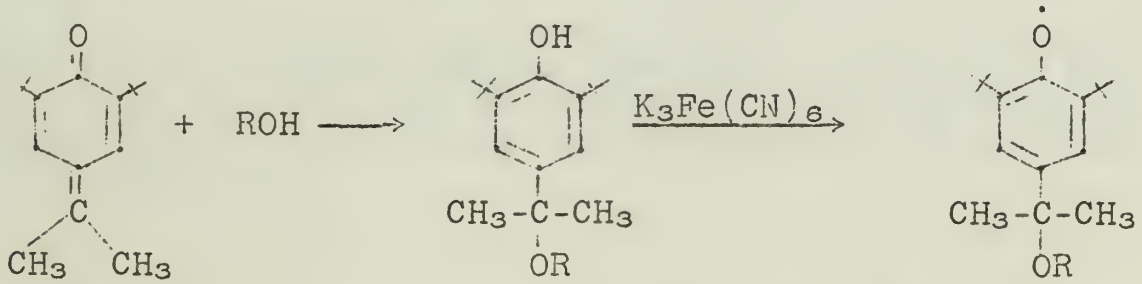
Other phenoxy radicals containing α-hydrogens dissociate in a different way. Reduction with alkaline ferricyanide of 4-isopropyl-2,6-di-t-butylphenol and of 4-s-butyl-2,6-di-t-butylphenol yielded deep blue solutions (31). Exposure to oxygen yielded peroxides of structure similar to tri-t-butylphenoxy peroxide. In the absence of oxygen, however, further dehydrogenation of the phenoxy compounds to quinone methides occurred after standing a short time:



R = CH_3, C_2H_5

The reaction is analogous to the oxidation of hydroquinones to quinones via the semiquinones.

Reaction of the quinone methides with simple alcohols yielded 4-dimethylalkoxymethyl-2,6-di-t-butylphenols which in turn can be oxidized to blue phenoxy radicals of stability comparable to tri-t-butylphenoxy (28,31):



R = CH_3, C_2H_5

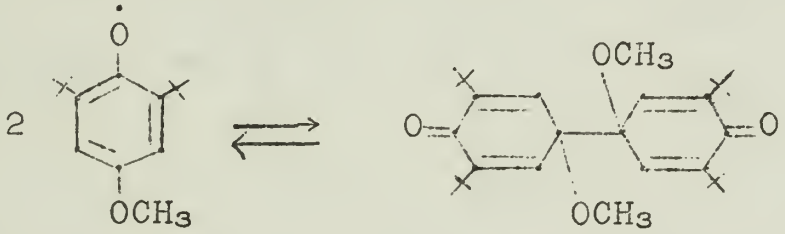
These phenoxy radicals react with oxygen to produce the usual peroxides.

B. Alkoxyphenoxy Radicals

Replacing the para alkyl group with an alkoxy group was found to yield a second series of stable phenoxy radicals. In contrast to the blue tri-alkyl compounds, the new radicals are red. Although replacement by an alkoxy group reduces the steric hindrance, radical stability is maintained by an oxonium ion resonance structure not possible in the tri-alkylphenoxy radicals:

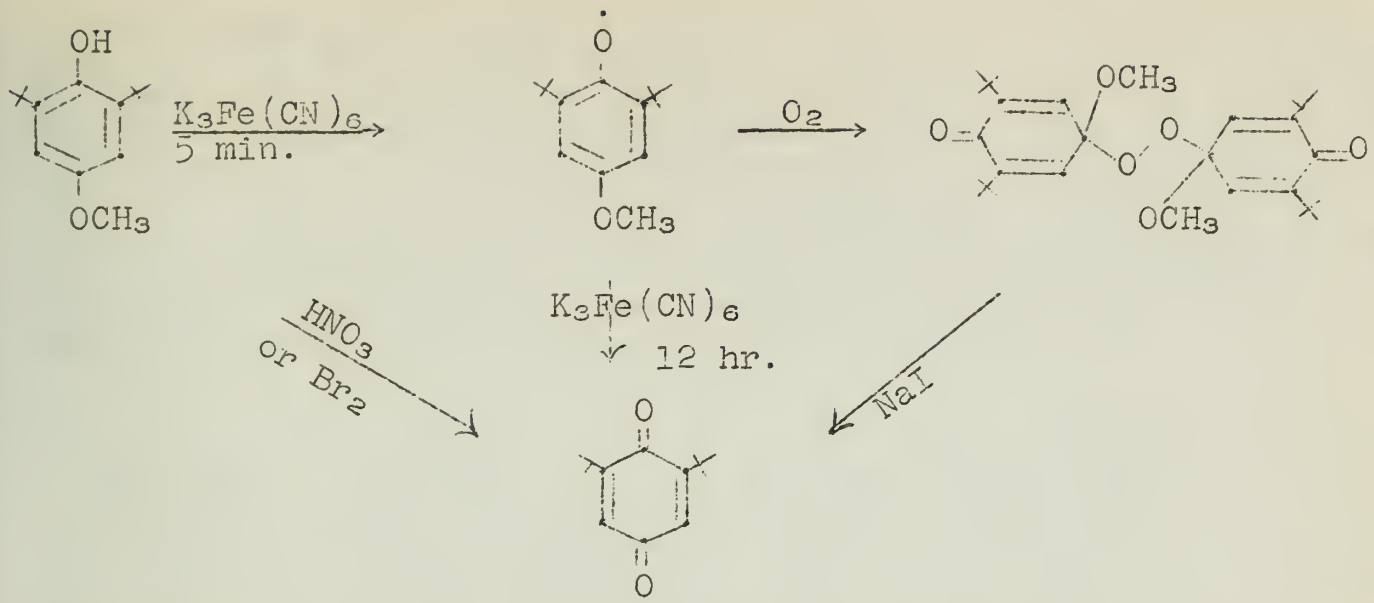
The compounds prepared included R = CH_3 (28,32), R = C_2H_5 (28), and R = $C(CH_3)_3$ (25,28). The radicals 4-methoxy- and 4-t-amyloxy-2, 6-di-t-amylphenoxy were also prepared (28).

The 4-methoxy-2,6-di-t-butylphenoxy, due to reduced steric hindrance at the para position, can dimerize readily. Investigation confirms that the radical and dimer exist in equilibrium:

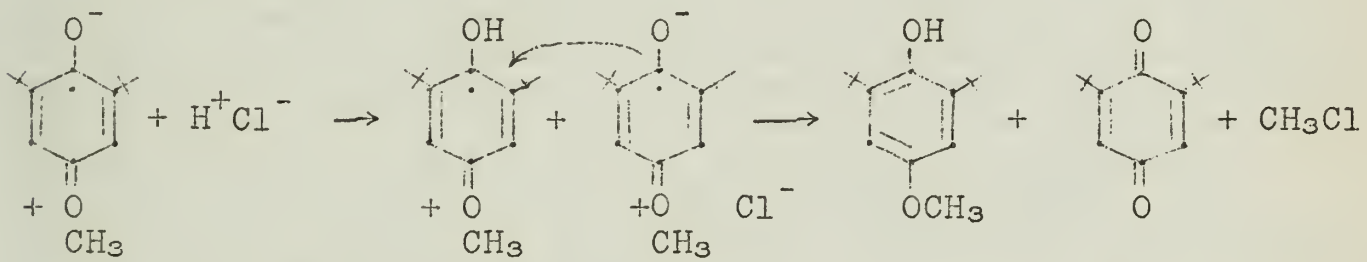


Although magnetic susceptibility measurements show that a 3% solution in benzene contains only 73% of the compound as free radical, treatment with sodium iodide gives a quantitative release of iodine Upon removal of the solvent, the pure compound was obtained as a reddish-black oil showing 27% free radical content at 20°C. Cooling the oil below -70°C. reduced the radical content to 13%. Such behavior is characteristic for free radicals existing in equilibrium with their dimers. Higher radical contents are present at higher temperatures. The infrared spectrum of the oil exhibited the characteristic strong band around 1590 $cm.^{-1}$.

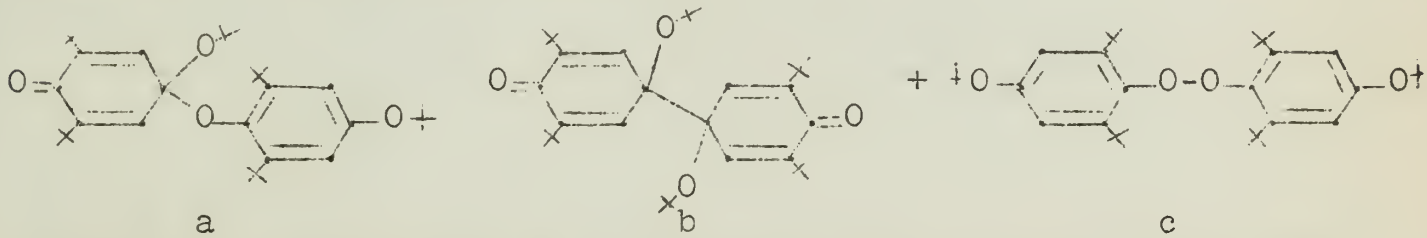
The 4-methoxy-2,6-di-t-butylphenoxy radical exhibited the usual behavior toward oxygen, resulting in a quinoid peroxide. Reduction of the peroxide, or oxidation of the starting phenol or phenoxy radical all resulted in the formation of 2,6-di-t-butylbenzoquinone (32):



The same quinone was one product of radical decomposition by aqueous hydrochloric acid. The reaction mechanism shown is similar to the electron transfer suggested for hydrochlorination of tri-t-butylphenoxy:



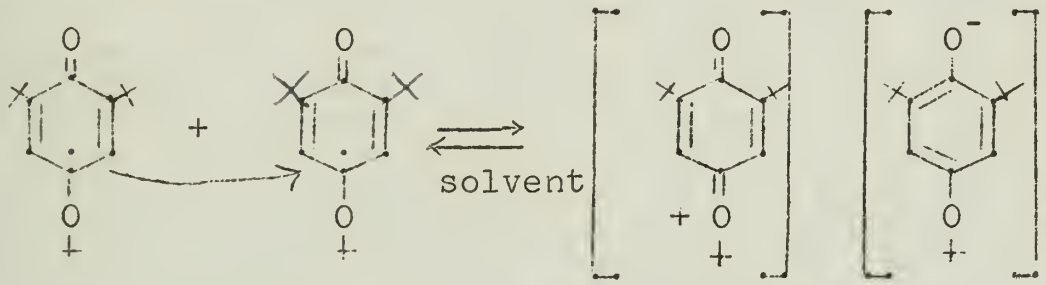
To study the effects of hindered dimerization, Müller replaced the methoxy group with t-butoxy (25). Oxidation of 4-t-butoxy-2, 6-di-t-butylphenol yielded a red-violet solution. Even as a 5.9% solution in benzene the product was essentially 100% free radical according to magnetic susceptibility measurements. In solution the radical showed the expected behavior toward sodium iodide by releasing I_2, and toward oxygen by forming a peroxide. However, attempted isolation of the pure radical resulted in formation of large, colorless, transparent crystals. These crystals were diamagnetic, yet instantly yielded the colored paramagnetic solution when dissolved in inert organic solvents. Infrared spectra of the crystals in KBr pellet exhibited the quinoid doublet at 1630 and 1650 $cm.^{-1}$. Several covalent dimers were suggested as the structure of the solid crystals:



a b c

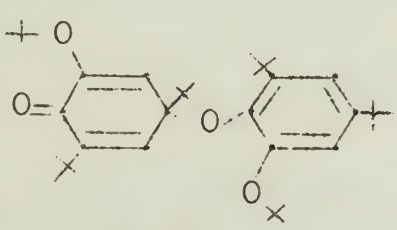
Compound a, a quinoid ether is rendered improbable on steric grounds, since its Stuart-Briegleb model is not possible. According to the models, compound b is just barely permissable, yet it is considered unlikely by comparison with the behavior of 4-methoxy-2,6-di-t-butylphenoxy dimer. Like this dimer, compound b

would be expected to exist in equilibrium with the corresponding radical. In fact, steric effects in Compound b would be expected to favor a dissociation to the radical greater than the 27% found in pure 4-methoxy-2,6-di-t-butylphenoxy dimer. The existence of 4-t-butoxy-2,6-di-t-butylphenoxy dimer as colorless diamagnetic crystals thus throws doubt upon formulation b. Formulation as the peroxide c does not explain the appearance of the quinoid band in the infrared spectrum. The elimination of these covalent structures leads Müller to the proposal that the dimer is an oxonium phenolate, formed by electron disproportionation:

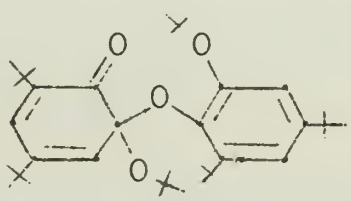


The reaction is analogous to the disproportionation of a semiquinone into quinone and hydroquinone. Such electron disproportionations, although characteristic of inorganic redox reactions, are less common in organic chemistry. Similar electron disproportionation, however, has been supported by extensive experimental and theoretical arguments in the case of several organic nitrogen radical dimers (33). The present reaction can be viewed as a "completed charge transfer" with the product representing a limiting case of the Mulliken charge transfer complex. The instantaneous solution of the colorless diamagnetic crystals to form an intensely colored paramagnetic solution is in accord with an electron transfer mechanism.

Shifting the t-butoxy group to the ortho position results in a radical of low stability (34). Indeed, a blue-green solution is formed upon treatment of 2-t-butoxy-4,6-di-t-butylphenol with alkaline ferricyanide. However, at room temperature magnetic susceptibility measurements on a 5.5% benzene solution indicate only 2% free radical content. Even at 65°C. the solution contains only 26% radical. Concentration of the solution affords yellow crystals which are diamagnetic and have IR bands at 1650 and 1680 $cm.^{-1}$ (quinoid) in KBr. The location of the t-butoxy group in the ortho position allows formulation of two non-hindered covalent dimers:



a



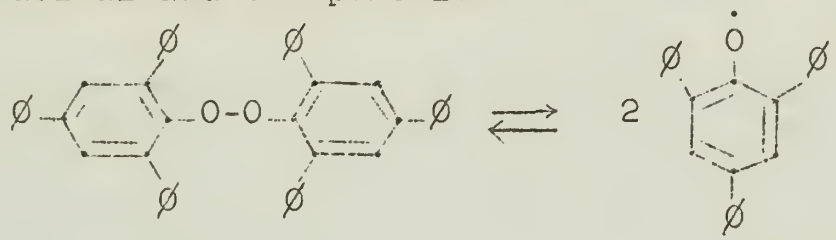
b

Distinction between formulations a and b has not yet been possible; however b is sterically more favorable. An oxonium phenolate structure is not definitely excluded for the dimer, but the evidence here is not so suggestive of it as in the case of 4-t-butoxy-2,6-di-t-butylphenoxy dimer.

C. Phenoxy Radicals Stable Toward Oxygen

The radicals discussed so far have shown high reactivity with molecular oxygen to form peroxides. Thus the reactions had to be conducted under an inert atmosphere. A high degree of steric blocking in the ortho and para positions appeared necessary to lessen the tendency toward dimerization. Although resonance was shown to promote stabilization, steric hindrance was considered of prime importance.

With the preparation of 2,4,6-triphenylphenoxy, resonance was shown to play a more important role (35), especially in reducing reactivity toward oxygen. Ferricyanide oxidation of 2,4,6-triphenylphenol yields a deep red solution totally inert to oxygen and showing no decrease in oxidizing power even after standing for one week. Concentration of the solution gave oxygen-stable crystals, soluble in organic solvents to give again the red solution. The crystals exist as the radical dimer, probably a peroxide involving the phenoxy oxygens. Attack on the phenoxy oxygen is favored by absence of steric hindrance in the ortho positions. At the same time, attack at the para carbon is presumably discouraged because disubstitution there would force the phenyl group out of resonance coplanarity. The complete inertness of the radical solutions toward oxygen provides further evidence against attack at the para position. In solution an equilibrium is expected between the radical and the peroxide:

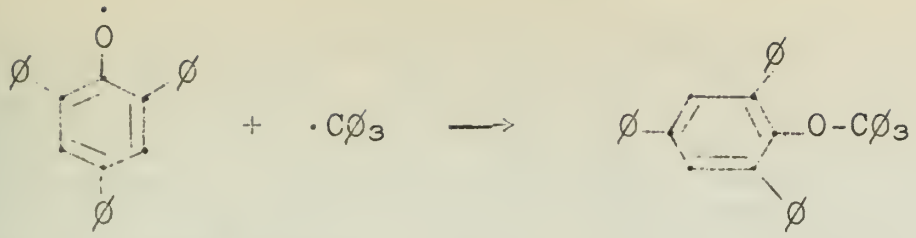


a b

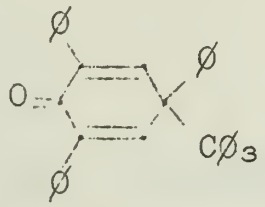
Heating the solution increases the color intensity, corresponding to driving the equilibrium to the right. The radical concentration was determined by taking advantage of the anti-Beer's Law behavior of the radical in carbon disulfide. As the solution was diluted, the molar extinction coefficient increased. Below 1.3×10^{-5} M (based on peroxide) the compound is almost entirely free radical. Measurement of extinction coefficients at several higher concentrations enabled calculation of the equilibrium constant for peroxide-radical formation:

$$K_{CS_2} = \frac{[b]^2}{[a]} = 2.4 \times 10^{-5} \text{ at } 20^\circ C$$

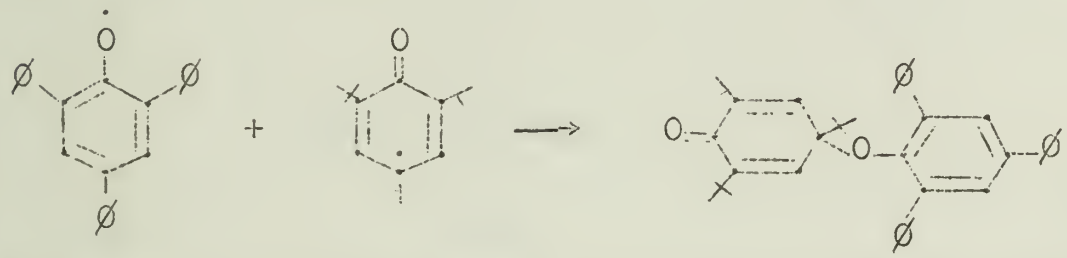
Triphenylphenoxy is a powerful oxidizer and readily reacts with H_2(Pt catalyst), hydroquinone, and various phenols, even tri-t-butylphenol. Triphenylphenoxy also reacts with other organic free radicals:



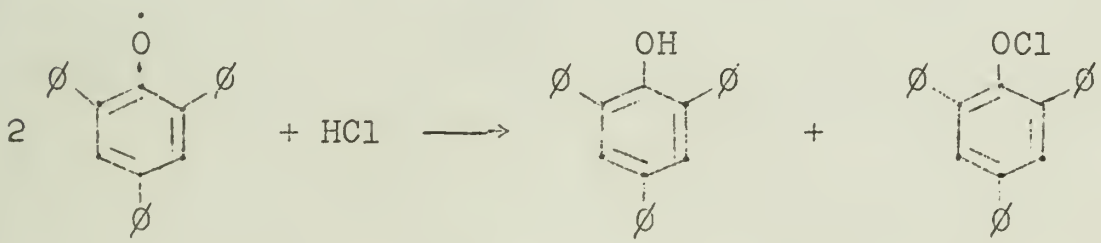
The colorless product of the reaction is stable to heating with hydrogen iodide for 3 hours. Such stability would not be expected of the quinoid compound that would be formed if the coupling involved the 4-carbon of the phenoxy radical:



A stable product is also formed by reaction of triphenylphenoxy with tri-t-butylphenoxy:

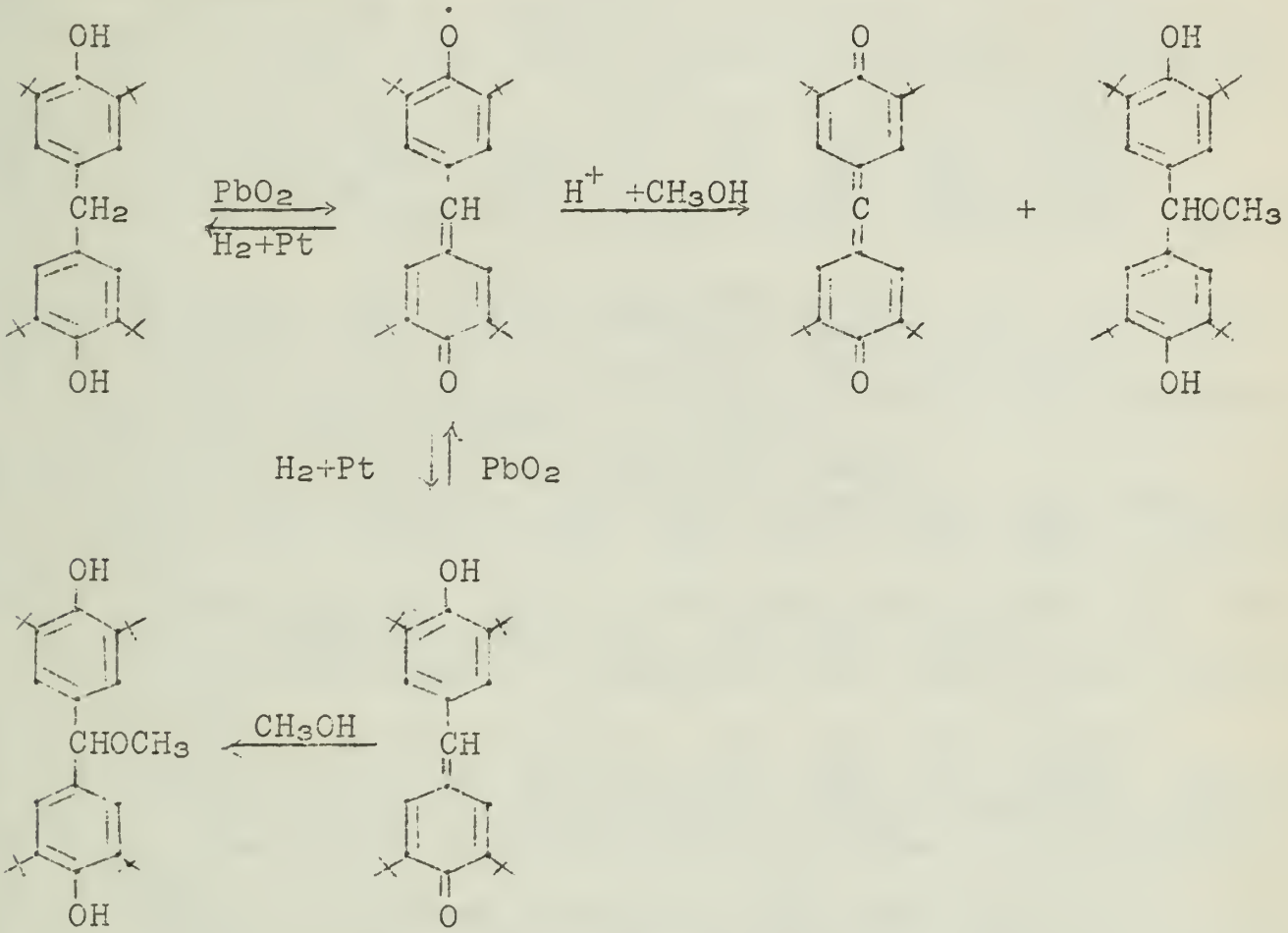


Formulation of the compound as a peroxide is unlikely because the product shows no tendency to dissociate at room temperature. The proposed structure is in accord with the reactivity of the 4-carbon in tri-t-butylphenoxy and of the phenoxy oxygen in triphenylphenoxy. Reaction of triphenylphenoxy with hydrogen halides probably involves attack only at the oxygen atom:



A second oxygen-stable phenoxy radical was recently prepared independently by two investigators (36,37). The compound is a derivative of bis(3,5-di-t-butyl-4-hydroxyphenyl) methane. Although the initial phenol possesses an α-hydrogen, a stable radical is formed by the eventual removal of 3 hydrogens.

Either alkaline ferricyanide or lead dioxide could be used to oxidize the phenol. The yield was 95% of dark blue crystals. The compound is reportedly stable for 3 months as crystals, or for 3 days in solution. When decay did occur, it was not by reaction with oxygen. Treatment with base, however, yielded a second radical (structure not given) which reacted rapidly with oxygen. The infrared spectrum showed the characteristic phenoxy band at 1572 $cm.^{-1}$. Both magnetic susceptibility and ESR confirmed the radical nature to the compound. Reactions are summarized in the following diagram:



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REACTIONS OF NITRONIUM AND ACETYLIUM SALTS

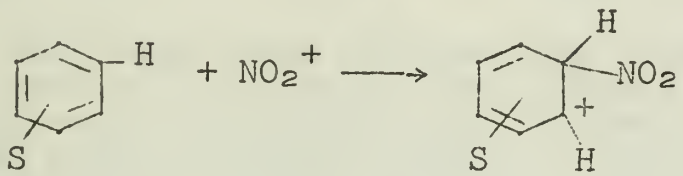
Reported by H. Babad November 25, 1957

INTRODUCTION

The topic of this seminar, nitration with nitronium salts (isolated as pure materials) and acetylation with solutions containing high concentrations of acyl perchlorates, might be cited as an advance in synthesis techniques based on theoretical advances in the study of reaction mechanisms. C. K. Ingold (1,2) and others have substantially shown that in aromatic electrophilic substitution, the active reactive species is usually a positively charged electrophile. For the case of aromatic nitration this is often the nitronium ion. Electrophilic aromatic substitution can thus be visualized as follows using the nitration as an example.

Chart I

1) $NO_2 \cdot \text{Anion} \rightleftharpoons NO_2^+ + \text{Anion}$

2) 

3) 

Ingold and co-workers (2) have shown that for easily nitrated materials step no. 1 can be rate controlling. The nitration of these compounds is zeroth order with respect to the aromatic compound used and dependent solely on the rate of formation of the reactive species. If step no. 2 is rate determining, we have a reaction which is first order, in the limiting case, with respect to the aromatic compound used and dependent on the reactivity thereof. The first part of this seminar will contain a discussion of nitration via pure ionic and covalent nitronium salts in the aromatic series and also of the addition of nitronium salts to substituted olefins.

Preparation and Properties of Nitronium Salts

Some of the materials containing the nitronium cation which are easily synthesized include gaseous nitryl chloride and nitryl fluoride and such crystalline substances as nitronium tetrafluoroborate, nitronium perchlorate and nitronium fluorosulphonate. The following equations are illustrative of their preparation:

Chart II

1. $ClSO_3OH + HNO_3 \rightarrow NO_2Cl\uparrow + H_2SO_4$ (ref. no. 5)
2. $NO_2Cl + AgF \rightarrow NO_2F + AgCl$ (ref. no. 6, no. 7)
3. $BF_3 + HF + NO_2Cl \rightarrow NO_2^+BF_4^-\downarrow + HCl$ (ref. no. 10)

4. $N_2O_5 + 3HClO_4 \rightarrow 2NO_2^+ClO_4^- \downarrow + H_3O^+ + ClO_4^-$ (ref. no. 9)
5. $N_2O_5 + 2SO_3 + F\text{-}SO_3H \rightarrow 2NO_2^+SO_3F^- \downarrow + H_2S_2O_7$ (ref. no. 9)

Both nitryl chloride and nitryl fluoride are gases. Nitryl fluoride has been shown to be a more stable and yet much more reactive reagent. Nitryl chloride slowly decomposes into elemental chlorine and nitrogen tetroxide upon standing. The other materials are crystalline white solids, melting above 200°C, and are stable if not exposed to excess moisture.

I. AROMATIC NITRATION WITH NITRONIUM SALTS

In the following table a comparison is made of the yields in aromatic nitration utilizing various conditions and reagents. The work on nitryl chloride was performed by Sears, et al (3,5); that on nitryl fluoride by Hetherington and Robinson (6); that on nitronium tetrafluoroborate by Olah, Kuhn and Mlinkó (10); that on the boron trifluoride nitrogen tetroxide complex by Bachman, et al. (11) and that on the antimony, silicon and phosphorus complex salts by Oláh, Kuhn and Mlinkó (10). See Table I for examples.

The work done seems to show that reaction of aromatics of intermediate activity gives better and cleaner yields under milder conditions when a nitronium salt is used than when the classical mixed acid techniques are applied. Nitryl chloride, even with an enhancement of reactivity by the addition of a Lewis acid, is an inferior reagent to nitryl fluoride. The table seems to indicate that the best reagent is the ionic nitronium tetrafluoroborate. It has been postulated that the rate of nitration was directly proportional to the electronegativity of the anion (12) and this seems not to be contradicted.

One can divide the reactions of these nitrating agents into three categories.

A. Those which yield tars mostly with highly reactive aromatics. [Ingold (9) reports that mixtures of phenol and nitryl perchlorate are spontaneously inflammable.]

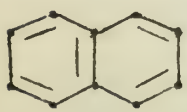
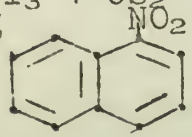
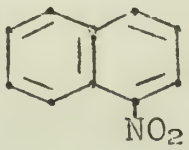
B. Those which give high yields (mostly with aromatic compounds of intermediate activity.)

C. Those which give little or no yields, even after long reaction times (mostly highly electronegitively substituted aromatics).

In closing, a prediction can be made that the method of nitration via nitronium salts, made in a wide spectrum of reactivities, will soon find wide application in aromatic nitration. The undeniable advantages of speed, mild, non-hazardous conditions and clean, high yields, more than offset the additional step needed to prepare the reagent (until it becomes commercially available.)

Table I

Aromatic Nitration Reactions With NO_2^+ Salts

Organic Substrate	Yields and Conditions for each Reagent					
	NO_2Cl	NO_2F	NO_2BF_4	$N_2O_4.BF_3$	Others	H_2SO_4 and HNO_3 (22,23)
Ø-H	Ø-NO_2-35% HF cat-70% $AlCl_3$+C_2S_2-89% all at 0°C	Ø-NO_2-65% meta$(NO_2)_2$Ø-57% 0°C	87% Ø-NO_2 0°C	40%-Ø-NO_2 0°C-1 week	$(NO_2)_2Si_1F_6$→ 93% Ø-NO_2 NO_2SbF_6→ 84% Ø-NO_2 NO_2PF_6→ 90% Ø-NO_2	Con H_2SO_4 and Con HNO_3 at 20°C-80% Ø-NO_2
CH_3-Ø	$AlCl_3$ + CS_2 47% O 24% P prod.	2,4-D.N.T. 55% 0°C	88% mononitro 0°C	———	———	
X-Ø x=halogen	$AlCl_3$ + CS_2 67% P 8% O prod.	60%-P trace-O	80-90% mononitro 0°C			Con H_2SO_4 + Con HNO_3 at 50-60°C p-BrØ-NO_2-65% plus some O.
NO_2-Ø	trace m-NO_2Ø-NO_2 at 0°C-m $AlCl_3$-CS_2	5% m-NO_2Ø-NO_2 at 0°C	85% m-NO_2 ØNO_2 with heating	m-NO_2-Ø-NO_2 7% 1 week at 15°C	$(NO_2)_2Si_1F_6$→ 82% m-NO_2 ØNO_2 with heating	Con H_2SO_4 + Fume HNO_3 at 50°C-70% m-NO_2Ø-NO_2.
	$AlCl_3$ + CS_2 31%  0°C= temp.	35%  0°C = temp.	93% mono-nitro product in Et_2O-10% Solu. 0°C	36 hs at 0°C 65% dinitro naphthalene (1-8, 1-5) isomers		Con H_2SO_4 + Con HNO_3 at 45°C→7% and nitro naphthlene Con H_2SO_4 and fume HNO_3 35% dinitro naphth. (1-5; 1-8) isomers

RO-Ø R_2N-Ø R=alkyl or H	tars	tars	traces of poly nitro derivatives plus tar even on dilut.		not ordinarily nitrated, yields tars
HOOC-Ø	low yields	no reaction	———	——	Con HNO_3 + Con H_2SO_4 5-18°C - 81% meta nitro benzoic acid
	——	——	14% with much tar		Acetic anhyride and con HNO_3 5-10°C - 75% yield

II. ADDITION OF NITRONIUM SALTS TO OLEFINS REACTION AND SYNTHETIC DATA

Price, et. al. (5) found that nitryl chloride added across the double bond in bromoethylene, methyl acrylate, acrylonitrile, and acrylic acid as well as its olefins.

Chart III

1. $Br\text{-}CH{=}CH_2 \xrightarrow[CCl_4]{NO_2Cl} Br\text{-}\underset{Cl}{CH}\text{-}CH_2NO_2$ (85%)

2. $CH_2{=}CHC(=O)\text{-}OCH_3 \xrightarrow{NO_2Cl}$
   - $O_2NCH_2\text{-}\underset{Cl}{CH}\text{-}C(=O)\text{-}OCH_3$ (75%)
   - $ClCH_2\text{-}\underset{Cl}{CH}\text{-}C(=O)\text{-}OCH_3$ (7%)
   - $O_2N\text{-}CH_2\text{-}\underset{OH}{CH}\text{-}C(=O)\text{-}OCH_3$ } (traces)
   - $O_2N\text{-}CH{=}CHC(=O)\text{-}OCH_3$ }

3. $CH_2{=}CHCN \xrightarrow{NO_2Cl}$
   - $O_2N\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}CN$ (76%)
   - $Cl\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}CN$ (13.5%)

$CH_2{=}CHCN \xrightarrow{Et_2O - NO_2Cl}$
- $Cl\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}CN$ (12%)
- $O_2N\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}CN$ (25%)
- $O_2N\text{-}CH{=}CH\text{-}CN$ (48%)

4. $CH_2{=}CHCOOH \xrightarrow{NO_2Cl} O_2N\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}COOH$ (71%)

5. $CH_2{=}CH\text{-}C(=O)\text{-}OCH_3 \xrightarrow{NO_2Cl} NO_2\text{-}CH_2\text{-}\underset{C(=O)OCH_3}{CH}\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}CO_2CH_3$

The last equation represents a side reaction resulting in the formation of methyl 2-chloro-4-nitro-methylpentanedioate. Regardless of the solvent used if any, ($CHCl_3$, CCl_4, Et_2O), the direction of addition remained the same.

Compounds of formulas R,R'-C=CH_2 (4, 8) react to add nitryl chloride and the resulting product (20-40% yields) always contains

the nitro attached to the terminal methylene group [R,R'= hydrogen, alkyl, aryl, cycloalkyl and aralkyl.]

B. Bachman, et. al. (12) found that a solid complex made from nitrogen tetroxide and borontrifluoride [$N_2O_4.BF_3$] added to methyl acrylate in a manner similar to nitryl chloride. Conductivity and spectral data show that this compound is ionic and of structure $[BF_3 . NO_2]^- NO_2^+$.

MECHANISM ELUCIDATION

From the paths of the preceding reactions Price and co-workers (5) postulated the following mechanisms to explain the fact that nitryl chloride addition to olefins, regardless of the electronic influences of groups neighboring the double bond, always puts the nitro group on the terminal methylene group. Cleavage of nitryl chloride may be either heterolytic or homolytic.

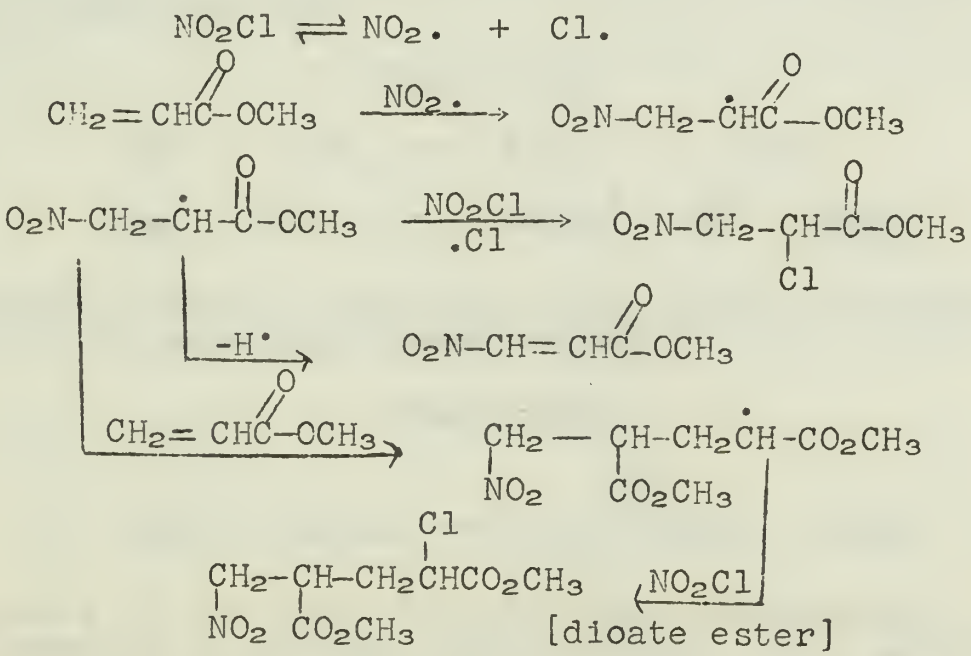
Chart IV

$$NO_2Cl \rightleftharpoons NO_2^+ + Cl^- \rightleftharpoons NO_2^- + Cl^+ \rightleftharpoons N_2O_4 + Cl_2$$

$$2NO_2Cl \rightleftharpoons 2NO_2\cdot + 2Cl\cdot \rightleftharpoons N_2O_4 + Cl_2$$

By considering the possible modes of cleavage of the reagent, contrasted to the specificity of addition direction in the olefinic compounds tested, the authors ruled out a heterolytic mechanism for electronegatively substituted olefins. This mechanism is impossible because nitryl chloride addition to both electronegatively and electropositively charged double bonds is in the same direction. The following mechanism utilizing homolytic cleavage followed by subsequent addition processes was suggested by the authors.

Chart V



It would seem that this mechanism is plausible.

The boron trifluoride-nitrogen tetroxide complex has been shown to decompose slowly into N_2O_4 and BF_3 so the similarity of its addition to methyl acrylate to that of nitryl chloride may be explained as the addition of homolytically cleaned nitrogen tetroxide to the double bond.

Though much work has been done on these reactions, many more experiments are needed before we can extend bottled nitrating agents to the field of olefin additions.

III. AROMATIC ACYLATION WITH SOLUTIONS OF PERCHLORATE SALTS

INTRODUCTION

In 1937 Hammett and Treffers (20) found evidence for the presence of mesitoylium ion from the heterolysis of the intermediate mesitoic acidium ion formed when mesitoic acid was dissolved in solvent sulfuric acid.

Chart VI

$$C_6H_2Me_3COOH + H_2SO_4 \longrightarrow C_6H_2Me_3COOH_2^+ + HSO_4^-$$

$$C_6H_2Me_3COOH^+ \longrightarrow C_6H_2Me_3\overset{\overset{O}{\parallel}}{C}^+ + H_2O$$

This was confirmed by cryoscopic data. Less highly substituted benzoic acids were only partially heterolyzed to benzoylium ions.

It was claimed by Gillespie (19) in 1950 via cryroscopic measurements that the addition of acetic acid to solvent sulfuric acid gave a freezing point depression consistent with the formation of the acetic acidium ion. The addition of acetic anhydride to sulfuric acid gave a freezing point depression consistent with the formation of acetylium ion.

Chart VII

$$HOAc + H_2SO_4 \longrightarrow AcOH_2^+ + HSO_4^-$$

$$Ac_2O + 2H_2SO_4 \longrightarrow AcOH_2^+ + Ac^+ + 2HSO_4^-$$

This cryrosopic evidence also seems to be perfectly consistent with the formation of protonated acetyl sulfate.

Chart VIII

$$Ac_2O + 3H_2SO_4 \longrightarrow CH_3\text{-}\overset{\overset{OH}{\overset{+}{\parallel}}}{C}\text{-}OSO_3H + AcOH_2^+ + 2HSO_4^-$$

H. Burton and P. F. G. Prail (13, 14) then experimented on the acylation reaction in strongly acidic media. These authors reacted anisole with acetic and perchloric acids in equimolar amounts and containing enough acetic anhydride to destroy the 2.2 moles per liter of water present in commercial 2% perchloric acid. They reported that no reaction occurred after 22 hours at room temperature.

When more acetic anhydride was added, acetylation took place rapidly due to the formation of acetyl perchlorate. Thus the acetylation reaction seemed to be due to an electrophilic attack on the aromatic compound by acetylium perchlorate or acetic anhydridium perchlorate as follows.

Chart IX

$$Ac.ClO_4 + Ar\text{-}H \longrightarrow Ar\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 + HClO_4$$

$$Ac_2OH.ClO_4 + Ar\text{-}H \longrightarrow Ar\overset{\overset{O}{\|}}{C}\text{-}CH_3 + AcOH + HClO_4$$

It had been previously shown that acetic acidium perchlorate doesn't give acylation, and it will be later shown that the acetic anhydridium perchlorate is a much less reactive acylating agent than the acetylium perchlorate. Under the conditions of the above reaction it was found that an increase in the amount of acetic anhydride in the system led to increased yields of p-acetyl anisole.

REACTIONS OF ACYL PERCHLORATE SOLUTIONS

Burton and Prail (15-18) next prepared and reacted concentrated solutions of acetylium perchlorate with anisole, meta-xylene, toluene and benzene. The reagent was prepared by the quantitative reaction of acetyl chloride with silver perchlorate in nitro methane. The results obtained are shown in Table II.

The reactivities of these aromatics toward acylation seem to fall in the same order as do their reactivities toward nitration; (anisole > meta-xylene > toluene > benzene). In all cases the yield was consistent with the stoichiometric amount of acetyl perchlorate when no acetic anhydride was present. When acetic anhydride was added, the total amount of acylation product, whether the main reaction product or the side products, was stoichiometrically greater than the amount of acetyl perchlorate originally present. The following set of reactions has been postulated, as first order approximation, to explain these results.

Chart X

$$1)\ {}_S\!\not{\phi}\text{-}H + AcClO_4 \longrightarrow {}_S\!\not{\phi}\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 + HClO_4$$

$$2)\ HClO_4 + Ac_2O \rightleftharpoons Ac_2OH.ClO_4 \rightleftharpoons AcClO_4 + AcOH$$

Probable equations for the production of β diketones, the principal side products are:

$$3)\ R\text{-}H + AcClO_4 \longrightarrow R\overset{\overset{O}{\|}}{C}\text{-}CH_3 + HClO_4 \xrightarrow{Ac^+} R\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_2\overset{\overset{O}{\|}}{C}\text{-}CH_3$$

$$4)\ Ac_2O + AcClO_4 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}\text{-}CH_2\overset{\overset{O}{\|}}{C}.ClO_4 \xrightarrow{R\text{-}H} + AcOH$$

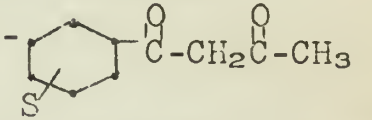
R= meta-zylene No. 3

R= benzene and toluene No. 4

Table .II .

Reactions of $AcClO_4$ with Aromatic Compounds

Conditons - 45 minutes at 0°-5°C

Aromatic	$AcClO_4$	Ac_2O	HOAc	Product	Side Reaction [Total]
1) Anisole-4 moles	1 mole	0 mole	0 mole	.84 mole p-acetyl anisole	none greater than 5%
-4 mole	1 mole	3 mole	0 mole	1.60 mole	none greater than 5%
-4 mole	1 mole	3 mole	12 mole	.18 mole	none greater than 5%
2) meta-xylene-4 mole	1 mole	0 mole	0 mole	.86 mole 1-acetyl 2,4-dimethyl benzene	none greater than 5%
-4 mole	1 mole	3 mole	0 mole	1.06 mole	β diketone- 
-4 mole	1 mole	3 mole	7 1/2 mole	.18 mole	none greater than 5%
3) 1-acetyl-2,4-dimethylbenzene-	1 mole	0 mole	0 mole	β-diketone	polymeric, intractible
1 mole acetophenone	1 mole	0 mole	0 mole	β-diketone	material
4) toluene-4 mole	1 mole	0 mole	0 mole	.44 mole p-acetyl toluene	none greater than 5%
-4 mole	1 mole	3 mole	0 mole	greater than .44 mole	β-diketone formation
-4 mole	1 mole	0 mole	6 mole	less than .44 mole	little side reaction
5) benzene-4 mole	1 mole	0 mole	0 mole	.05 mole acetophenone	none greater than 5%
-4 mole	1 mole	3 mole	0 mole	.01 mole	much β diketone formed
6) Reagent Blank	1 mole	3 mole	0 mole	after hydrolysis poly-aceto acetic acids	

This seems to be in accordance with experiments No. 3 and No. 6 in table II. Equations No. 1 and 2 in chart X follow from the remainder of the experiments if the products are taken into consideration. Large concentrations of acetic acid seem to surpress the reaction, which would seem to indicate that acetic anhyridium perchlorate is a weak acylating agent (chart X eqn. No. 2).

H. Burton and P. F. G. Prail (13, 18) have further shown that with mixtures of acetic acid and perchloric acid acylation can be obtained if the mixture is dehydrated with phosphorus pentoxide.

Chart XI

$$HClO_4 + AcOH \longrightarrow AcOH_2ClO_4$$

$$AcOH_2ClO_4 + PrO_5 \longrightarrow 2HPO_3 + AcClO_4$$

Substituted benzoylium perchlorates have also been used successfully as acylating agents by Burton and Prail (16, 17, 18).

Though there is little doubt as to the ultimate synthetic applicability of the technique of acylation via solutions of perchlorates, no one has yet proven the nature of this reagent conclusively. Burton and Prail have postulated reaction paths on the basis that acetyl perchlorates are ionic substances, but the reaction products obtained experimentally would be the same if formed by the attack of covalent acetyl perchlorate on the aromatic.

As a final note, it is interesting to notice that crystalline acetyl perfluoroborate has been prepared by Seel (21) from BF_3 and acetyl fluoride. The properties of this material toward acylation have not yet been determined.

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ALKALINE NITRATION

Reported by R. G. Woolford December 2, 1957

INTRODUCTION

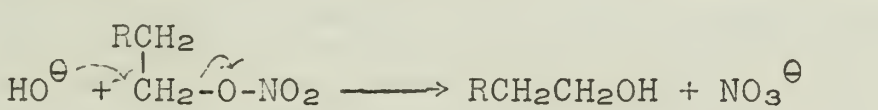
The introduction of a nitro group into an organic molecule almost always requires the use of a highly acidic reagent. This requirement limits the number and type of compounds that can be nitrated because of the sensitivity of some compounds to acids. This seminar will deal with the search for reagents which can effect nitration under neutral or alkaline conditions. As a preliminary to this discussion, mechanism studies on the alkaline hydrolysis of nitrate esters will be reviewed briefly so as to provide some background for the work to follow.

ALKALINE HYDROLYSIS OF NITRATE ESTERS

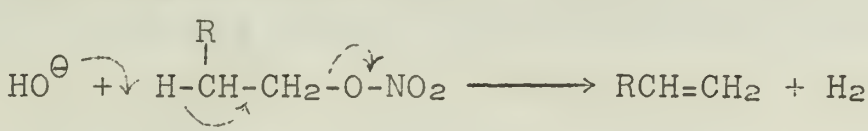
Early work (1) gave a very confused picture of the reactions which occur in alkaline hydrolysis of nitrate esters. The only clearly established point was the occurrence of reactions other than simple fission to alcohol and nitric acid, and the general view (later disproved) was that such side-reactions, including nitrite formation arose from subsequent oxidation of the alcohol by the nitric acid.

To explain the formation of alcohols, olefins, carbonyl derivatives and nitrite ion, Baker and Easty (2,3,4) made an analogy with the picture of nucleophilic substitution and elimination reactions of alkyl halides which has resulted from the extensive investigations of Ingold and Hughes (5,6). Baker suggested that hydrolytic fission of organic nitrates involves the following three simultaneous reactions: (for simplicity, only the bimolecular mechanisms are depicted, although it is evident that, under suitable structural and environmental conditions, the corresponding unimolecular mechanisms may function).

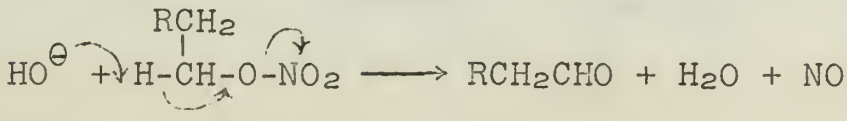
I. Nucleophilic Substitution (yielding alcohol)



II. β-Hydrogen Elimination (yielding olefin)



III. α-Hydrogen Elimination (yielding carbonyl + nitrite)



In reactions I and II it was assumed that fission occurred at the carbon-oxygen linkage of the nitrate group and in III at the oxygen-nitrogen bond.

A thorough kinetic study on a series of nitrates indicated for reaction I a bimolecular mechanism for the primary and secondary nitrates and a unimolecular mechanism for the tertiary compounds. Due to the similarity of the hydrolyses of alkyl halides and alkyl nitrates, Baker assumed that the substitution reaction (I) occurred by attack exclusively on carbon, and did not consider an attractive alternate mechanism for the substitution reaction I, i.e., analogous to that usually ascribed to carboxylic esters (7,8). [except in a few cases where steric hindrance gives rise to alkyl-oxygen cleavage, most esters are hydrolyzed in alkali by acyl-oxygen fission (9)], whereby nitrogen-oxygen cleavage as in IV could occur rather than carbon-oxygen cleavage as in I.

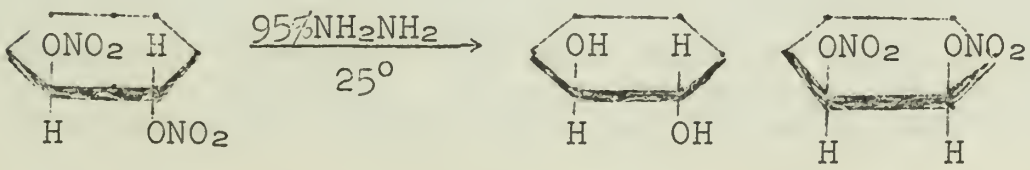
IV. $HO^{\ominus}$ + O_2N-OR $\longrightarrow$ $HONO_2$ + $\overset{\ominus}{O}R$ $\longrightarrow$ $NO_3^{\ominus}$ + ROH

Two recent studies (10,11) have shown that in many cases IV does occur. Concerning themselves only with the substitution reaction, Anbar (10) studied the alkaline hydrolysis of nitrate esters in water enriched in O^{18}. In some cases, esters labelled with O^{18} were used in normal water. The formation of some labelled alcohol in reactions of n-butyl and n-octyl nitrates showed that substitution must have occurred partly by I, partly by IV. t-Butyl and triphenylmethyl nitrates reacted solely by I.

Cristol, et al., (11) showed by hydrogenolysis that (+)-2-octyl nitrate and (+)-2-octanol have the same configuration. Alkaline hydrolysis of (+)-2-octyl nitrate gave 2-octanol with mainly retention of configuration (88% (+) and 12% (-)). Similarly (-)-2-octyl nitrate gave 2-octanol which was 71%(-) and 29%(+). A bimolecular reaction by I would lead to inversion, while by IV retention would occur. Cristol assumed that inverted product did not arise by racemization and that the amounts of the optical isomers produced indicated the relative amounts of either carbon-oxygen or nitrogen-oxygen fission.

In neutral solution (+)-2-octyl nitrate gave mainly (-)-2-octanol (85%(-) and 15%(+)). Thus a displacement on carbon (path I) predominates in neutral solution.

In view of these results, the work of Baker should be re-interpreted in terms of reaction path IV as a possibility in addition to I-III. Other work (12,13,14,15) on the reduction of alkyl nitrates with hydrazine and with alkaline hydrosulfides showed that nitrogen-oxygen cleavage as in IV mainly occurs. For example, trans 1,2-cyclohexanediol dinitrate gave only trans glycol, while only cis glycol could be obtained from cis dinitrate.



Thus we may conclude that, under alkaline conditions, nitrate esters are borderline compounds with reasonably comparable abilities to undergo alkyl-oxygen cleavage like alkyl halides and nitrogen-oxygen cleavage analogous to most carboxylic esters.

USE OF NITRATE ESTERS

N-NITRATION

Until recently only three good methods for the preparation of nitramines existed:

(a) The oxidation of nitrosamines to nitramines (16). Using peroxytrifluoracetic acid, pure secondary nitramines can be obtained in almost quantitative yield.

(b) The chloride ion catalyzed direct nitration of amines (17,18) using a nitric acid-acetic anhydride mixture.

(c) The nitrolysis of dialkylamides (19):

$$R'CONR_2 + HNO_3 \longrightarrow R'COOH + R_2NNO_2$$

These methods all possess the disadvantages of involving strongly acidic reagents and in general are applicable only to the preparation of secondary nitramines (only (b) will yield primary nitramines).

The use of alkyl nitrates to bring about nitration of amines was investigated as early as 1905. Angeli (20) isolated a poor yield of phenylnitramine from the reaction of aniline and ethyl nitrate in the presence of sodium in ether.

$$C_6H_5NH_2 + EtONO_2 \xrightarrow[\text{ether}]{Na} C_6H_5NHNO_2 + EtOH$$

This reaction was also carried out (21) using ethoxide ion in place of sodium in ether.

However, these reactions were not found to be general and were usually unsuccessful unless carried out in acid media (22). For example, the nitration of ethyl urea was achieved (23) by treatment of the urea with ethyl nitrate in sulfuric acid.

$$EtNHCONH_2 + EtONO_2 \xrightarrow{H_2SO_4} EtNHCONHNO_2 + EtOH$$

It was believed that efforts to nitrate amines with simple alkyl nitrates were failing because of competition from side reactions apparently taking place by nucleophilic attack on carbon. By weakening the oxygen-nitrogen bond (thus increasing the positive charge on nitrogen), the main reaction might be nucleophilic attack on nitrogen. As a preliminary experiment Emmons tried trichloroethyl nitrate with the following result (24).

$$Cl_3CCH_2ONO_2 + 2R_2NH \longrightarrow HCCl_3 + R_2NNO + R_2NCHO + H_2O$$

Significantly no alkylation was noted. This reaction can be explained in terms of α-elimination according to the mechanism of Baker.

(a) Alpha elimination: $R_2NH + Cl_3CCH_2ONO_2 \longrightarrow R_2NH_2^{\oplus} + Cl_3CCHONO_2^{\ominus}$

$Cl_3CCHONO_2^{\ominus} \longrightarrow Cl_3CCHO + NO_2^{\ominus}$

(b) Nitrosation: $R_2NH_2^{\oplus} + NO_2^{\ominus} \longrightarrow R_2NNO + H_2O$

(c) Formation of N,N-dialkyl formamide:

$$Cl_3CCHO + R_2NH \longrightarrow [Cl_3CCH(OH)(NR_2)] \longrightarrow HCCl_3 + R_2NCHO$$

Reaction (c) is supported by a study (25) of the reaction of chloral with secondary amines, yielding the formyl derivative of the amine as primary product.

To avoid this alpha-elimination reaction, Emmons (26) tried the little known ketone cyanohydrin nitrates. Acetone cyanohydrin nitrate was easily prepared in 70% yield by adding acetone cyanohydrin to white fuming nitric acid in acetic anhydride at 0°C.

This reagent was found to be excellent for converting aliphatic and alicyclic amines to nitramines under alkaline or neutral conditions (Table I). An excess of amine was used to remove the hydrogen cyanide and acetone produced in the reaction.

$$R_2NH + CH_3C(ONO_2)(CN)CH_3 \longrightarrow R_2NNO_2 + CH_3COCH_3 + HCN$$

$$R_2NH + HCN + CH_3COCH_3 \longrightarrow R_2NC(CH_3)_2CN + H_2O$$

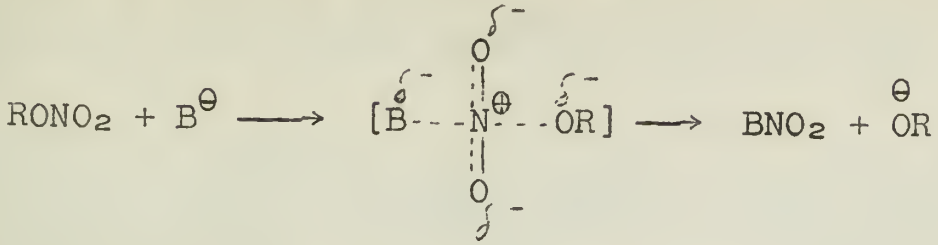
TABLE I

PREPARATION OF NITRAMINES USING ACETONE CYANOHYDRIN NITRATE

Nitramine	Yield (%)	Nitramine	Yield (%)
Dimethyl	76	Nitromorpholine	81
Diethyl	60	Nitropyrrolidine	60
Di-n-propyl	42	n-Propyl	50
Di-n-butyl	54	n-Butyl	52
Diisobutyl	60	Isobutyl	54
Diisoamyl	64	n-Amyl	55
Mononitropiperazine	55	Isoamyl	54
Nitropiperidine	62		

Aromatic amines and aliphatic amines with branching at the α-carbon atom are unaffected by this reagent. The former probably fail to react due to their decreased basicity, while in the latter, steric interference of the alkyl groups can occur, hindering the nitrogen-nitrogen bond formation. Cyclic amines and dimethyl amine reacted most rapidly and in these compounds, steric hindrance is at a minimum.

In this type of reaction, the following transition state was postulated:



With ordinary nitrate esters, the reaction is simply a nucleophilic displacement on nitrogen with the leaving group contributing little driving force for nitration. With acetone cyanohydrin nitrate, the probable concerted fragmentation of the leaving group adds driving force to the reaction. Thus the reactivity of acetone cyanohydrin nitrate can be attributed to three things:

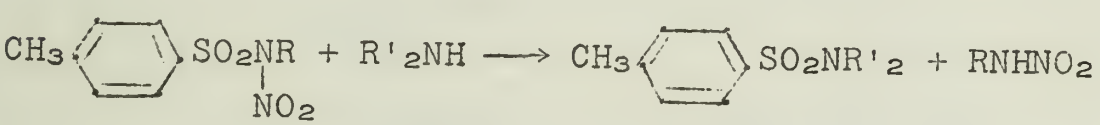
(1) the tertiary nature of the nitrate ester (i.e., lack of α-hydrogen atoms)

(2) the presence of an electronegative group which weakens the oxygen-nitrogen bond.

(3) the ease of decomposition of the cyanohydrin structure on nucleophilic attack which adds driving force to the reaction.

In the cases of trichloro-t-butyl nitrate and ethyl α-nitratoisobutyrate, both reagents fulfill the first two requirements but fail in the third and are therefore ineffective.

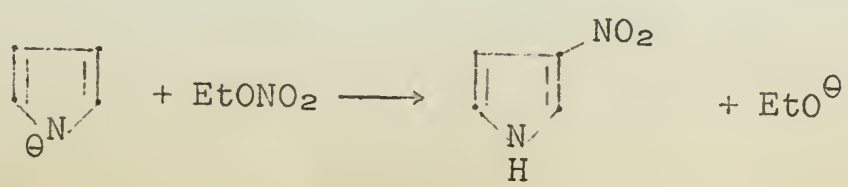
Other excellent reagents for preparing nitramines under alkaline conditions are N-nitrotoluenesulfonamides (27), prepared by treating the sulfonamide with nitric acid at 0°C.



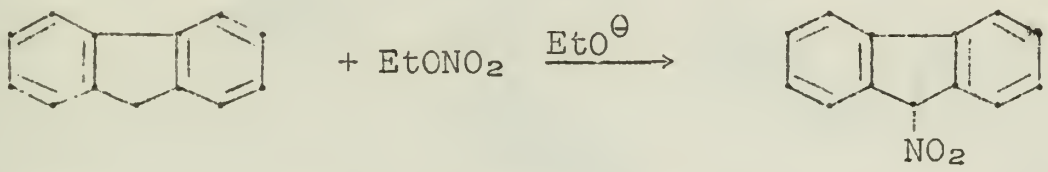
These reactions are carried out in acetonitrile and piperidine at room temperature and are general for primary nitramines with yields of 81-96%. Note that this is not a direct nitration of an amine but involves a rapid and nearly quantitative cleavage of the sulfur-nitrogen bond.

C-NITRATION

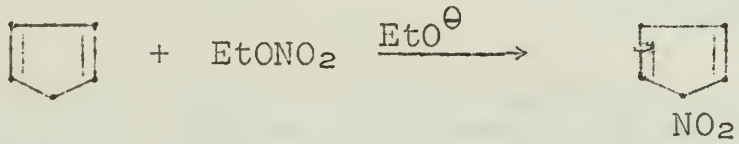
The sodium salt of pyrrole reacts with ethyl nitrate to yield β-nitropyrrole (28). This nitration is different from that of most aromatic systems, in that the nitration occurs under basic conditions. Reaction is assumed to occur by way of a nucleophilic attack by the pyrrole anion on the nitrate ester, displacing ethoxide ion.



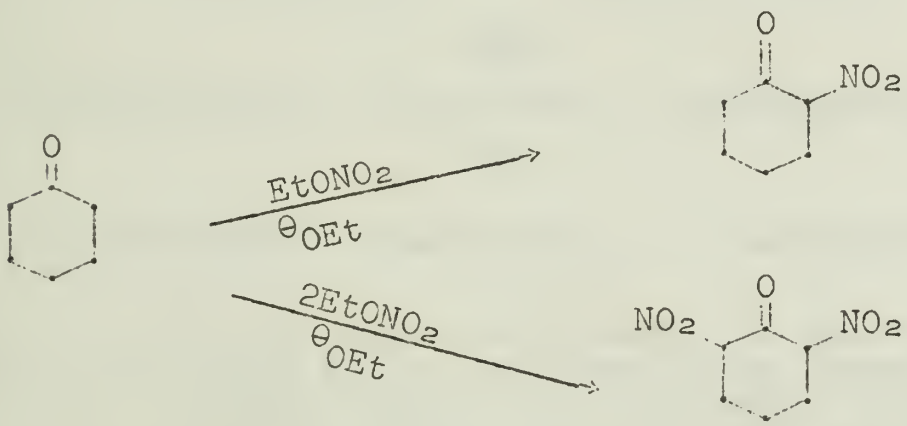
Compounds containing active methylene groups are readily nitrated by means of primary or secondary alkyl nitrates in the presence of ethoxide ion. Thus, fluorene gives 9-nitrofluorene in 70% yield by reaction with ethyl nitrate (29).



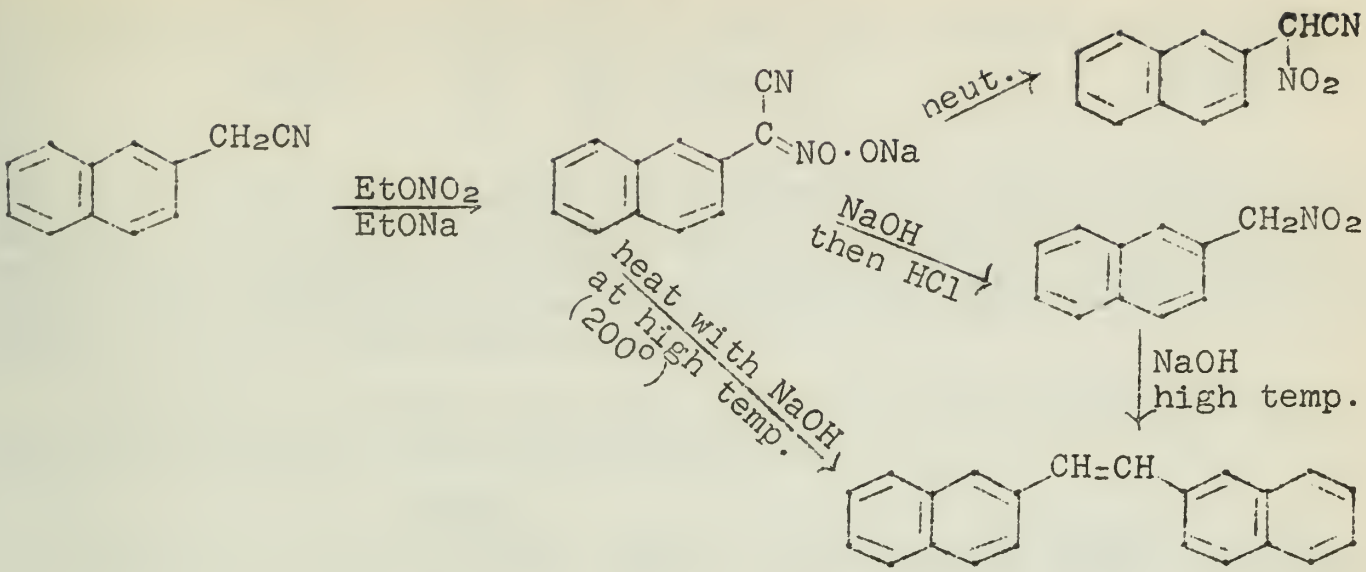
Cyclopentadiene could be nitrated in similar fashion (30) but no good examples of nitration of open-chain aliphatic compounds were found.



Other early work showed that arylacetic esters (31), arylacetonitriles (32,33) and certain cyclic ketones could be nitrated in this manner. For example, cyclohexanone could be reacted with ethyl nitrate to yield either a mono- or a dinitroderivative (39). Similarly 4-methylcyclohexanone gave a mononitroketone (35) while cyclopentanone yielded only the dinitrocompound (34).



In the cases of the cyclic ketones the yields were usually in the range 20-35%. Often in the nitration of various arylacetic acids, the products were hydrolyzed and decarboxylated to give routes to the corresponding arylnitromethanes, or they could be converted into the respective symmetrical stilbene derivatives. A typical example is found below.



Because of the success of the reactions of acetone cyanohydrin nitrate with amines, Emmons and Freeman (36,37,38) investigated the possibility of this reagent as an alkaline nitrating agent for active methylene compounds.

With this reagent diethylmalonate was nitrated in 45% yield. The best results were obtained by using sodium hydride as the base in tetrahydrofuran solution.

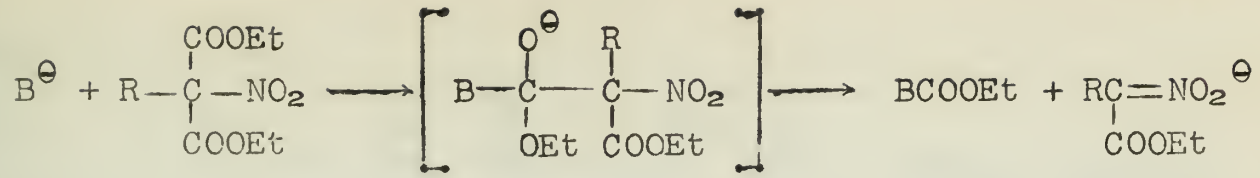
$$CH_2(COOEt)_2 \xrightarrow{NaH} Na[CH(COOEt)_2]$$

$$Na[CH(COOEt)_2] + CH_3\text{-}\underset{\displaystyle CN}{\overset{\displaystyle ONO_2}{\overset{|}{\underset{|}{C}}}}\text{-}CH_3 \longrightarrow NO_2CH(COOEt)_2 + NaCN + CH_3COCH_3$$

$$NO_2CH(COOEt)_2 + Na[CH(COOEt)_2] \longrightarrow NaO_2N{=}C(COOEt)_2 + CH_2(COOEt)_2$$

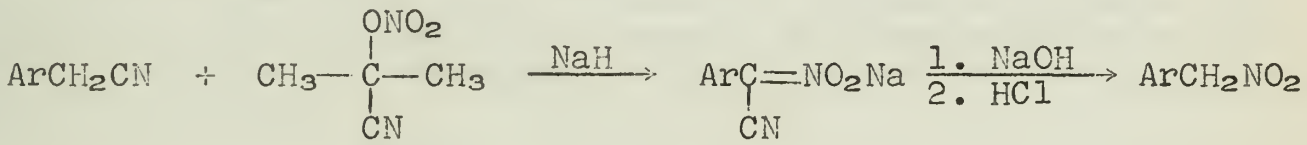
As can be seen, an excess of sodiomalonic ester is needed to ensure good yields as the reaction favors formation of the nitronate salt with the destruction of one equivalent of sodiomalonic ester. An excess of sodium hydride cannot be used as it degrades the nitromalonate to ethyl nitroacetate.

This degradation of nitromalonic ester by sodium hydride was used to provide a useful synthesis for α-nitroacetates which have become increasingly important in the synthesis of aminoacids. Previous methods for the production of nitroesters failed to give good yields of α-nitroacetates (39,40). The previous methods involved direct nitration of the malonic ester followed by ester group cleavage or by nitrosation of the malonic ester followed by oxidation. Acetone cyanohydrin nitrate in excess sodium hydride gave yields of 42-70% from the appropriate malonic or acetoacetic ester derivatives. This method is especially valuable for the preparation of α-nitroesters containing functional groups, such as aromatic rings, which would be attacked by the usual acidic nitrating mixtures.



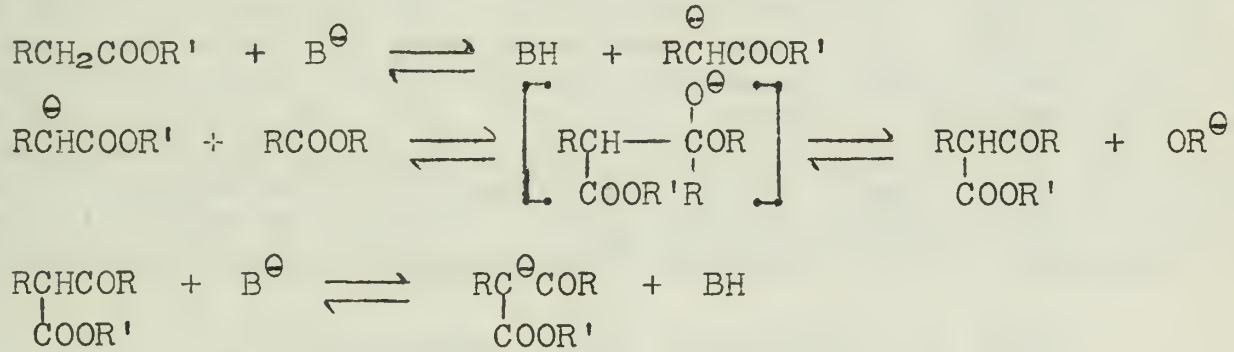
Hydride ion presumably causes this degradation since tricarbethoxymethane, which would have been formed from attack by sodiomalonic ester anion, was never obtained. The superiority of the nitronate anion over alkoxide ion as a leaving group probably accounts for the ease with which this reaction occurs.

Acetone cyanohydrin was also useful in the preparation of arylnitromethanes from arylacetonitriles.



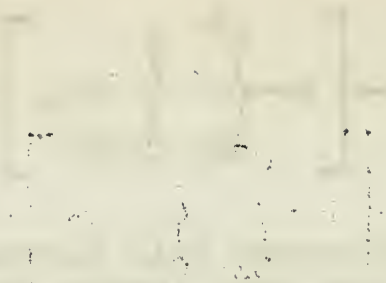
Phenylacetonitrile and o-chlorophenylacetonitrile react in this manner but no reaction occurs with less active methylene compounds, such as acetophenone and diethyl succinate.

The Claisen condensation may be used as a starting point for a discussion of the probable mechanism of alkaline nitration on carbon (41):

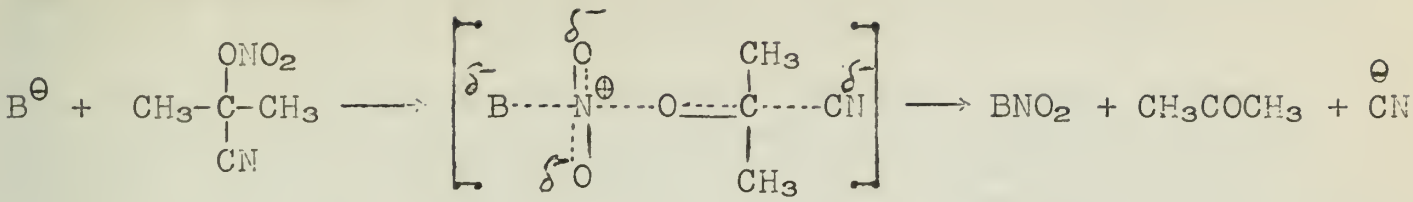


The essential difference between this reaction and that of alkyl nitrates lies in the difference between the carbonyl and the nitro group. Addition to either of these groups requires that the oxygen atoms absorb the negative charge. A carbonyl oxygen atom accepts it readily and hence is attacked by anions of widely varying base strength. The nitro group is resistant to addition since an intermediate of wide charge separation results. Thus the nitro group will react <u>additively</u> only with very reactive anions.

Alkaline nitration with simple alkyl nitrates thus follows the mechanism of the Claisen condensation very closely though only very reactive anions will react. However, the structure of the acetone cyanohydrin nitrate modifies this reaction so that an intermediate of the type formed in the second step of the Claisen condensation need not form. Instead it is thought that reaction occurs by nucleophilic displacement on nitrogen and thus negative charge is transferred from the attacking anion to the cyano group instead of



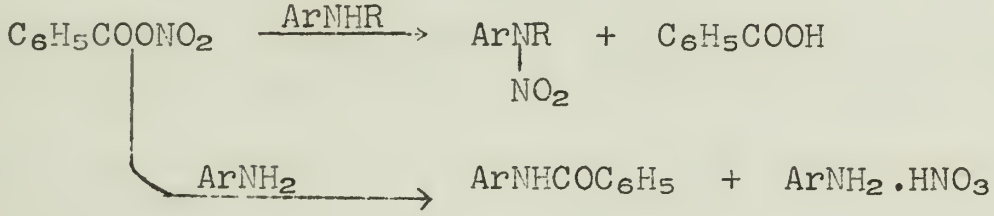
the nitro group.



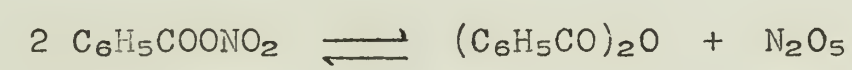
Such a picture explains the reactivity of acetone cyanohydrin nitrate toward anions that do not attack ordinary nitrate esters.

ACYL NITRATES

The study of acyl nitrates as alkaline nitrating agents has been limited since they show a tendency to explode. Francis (42, 43) reported that benzoyl nitrate reacts with secondary aromatic amines to produce the nitramine, but with primary amines only the amide was produced.

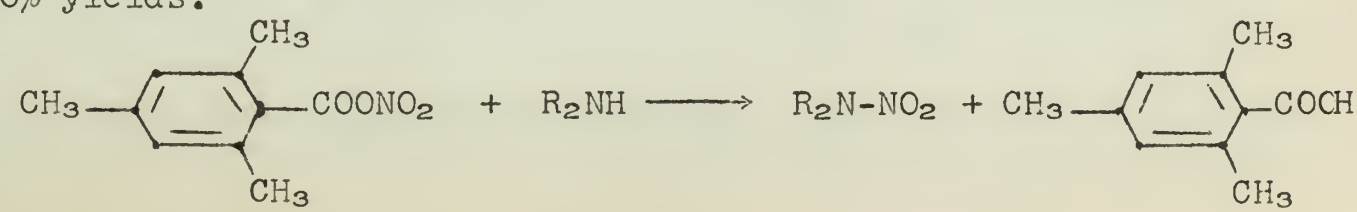


These results were confirmed and extended by Butler (44) who showed that aliphatic amines are acylated exclusively. Both benzoyl nitrate and acetyl nitrate have been used in the nitration of aromatic compounds, particularly benzenoid hydrocarbons and phenol derivatives (45, 46, 47). With this type of nitrating agent the ortho/para ratio of isomers formed is much higher than that produced in nitration involving nitric acid. Ingold (48) has shown in a kinetic study of nitration using benzoyl nitrate that nitrogen pentoxide is the nitrating species produced in the reaction.



This is believed to be true in the cases of acetyl nitrate, nitric acid in excess acetic anhydride and nitrogen pentoxide in acetic anhydride, all of which appear to yield the same system. Acetyl nitrate can be isolated from the reaction of nitrogen pentoxide with acetic anhydride. This mechanism of aromatic nitration appears to be quite different from that of amine nitration and the reader is referred to the references quoted for more details.

Mesitoyl nitrate has been used (49) in the nitration of secondary aliphatic amines to form the corresponding nitramines in 40-60% yields.



The reaction proceeded most readily with highly branched amines. Cyclic amines such as piperidine were nitrated but also underwent acylation leading to mixtures of the amide and nitramine.

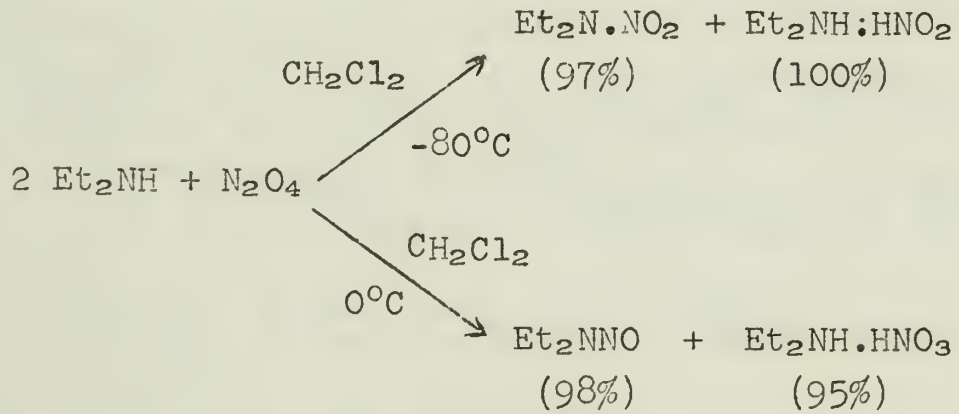
While secondary amines attacked mesitoyl nitrate almost exclusively at the nitro group, primary amines reacted at the carbonyl group, producing amides. The only example in which a primary amine was nitrated with mesitoyl nitrate was that of t-butyl amine. Thus it is apparent that the steric hindrance offered by the o-methyl groups was not sufficient to prevent reaction at the carbonyl group of mesitoyl nitrate when primary amines were used.

Pivalyl nitrate [$(CH_3)_3CCOONO_2$] and diethylacetyl nitrate [$(C_2H_5)_2CHCOONO_2$] have been tried (49) as alkaline nitrating agents but acylation of amines rather than nitration was observed.

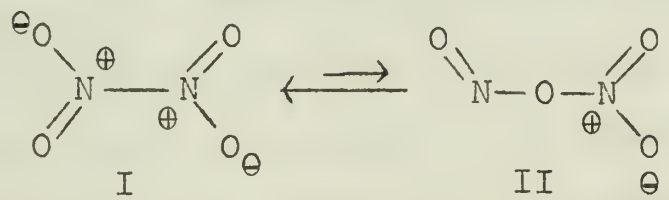
NITROGEN TETROXIDE

Most of the chemical reactions of nitrogen tetroxide involve nitrosation. Ammonia (50), primary aromatic amines (51) and alcohols (52) are nitrosated by nitrogen tetroxide but in no case is nitration observed. Nitration, as a primary reaction occurs only at low temperatures, and with reactants that are strong bases.

White and Feldman have found (53) that with a 1M solution of nitrogen tetroxide in methylene chloride at -80°C, a clean nitration reaction of secondary amines occurs. By raising the reaction temperature to 0°C, a clean nitrosation reaction occurs. The following are typical reactions.



The results were interpreted in terms of an equilibrium between two isomeric forms of nitrogen tetroxide, I being the predominant form.



The nucleophilic displacement of nitrite ion from I leads to nitration and the displacement of nitrate ion from II leads to nitrosation.

Nitrogen tetroxide was also extremely effective in nitrating alcohols to the corresponding nitrates, reaction being carried out at -80°C. A primary amine, hexyl amine yielded 53% of the desired nitramine at -80°C in addition to hexyl alcohol and hexyl nitrate.

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ARYLATION OF UNSATURATED COMPOUNDS WITH DIAZONIUM SALTS: THE MEERWEIN REACTION

Reported by Wayne Carpenter December 9, 1957

A. INTRODUCTION

The Meerwein reaction is the reaction between an aryl diazonium salt and an unsaturated compound to produce a new carbon-carbon bond between the aryl group and one of the olefinic carbons of the unsaturated compound. This seminar will not discuss the arylation of aromatic systems by diazonium salts.

Hans Meerwein (4), who was the first man to arylate acyclic α,β-unsaturated compounds by diazonium salts, is credited with the discovery of this reaction, although Kvalnes (2) and Wieland (3) had previously used diazonium salts to arylate quinones.

B. GENERAL REACTION PROCEDURE

The amine is diazotized at or near 0°C with sodium nitrite and excess hydrochloric acid. Sodium acetate is added in sufficient quantity to bring the resulting solution to a pH of 3-5. The unsaturated compound is usually dissolved in acetone, but other solvents such as pyridine, dimethyl sulfoxide, and acetonitrile, have also been used (50). The solution of the unsaturated compound is added to that of the diazonium salt and then cupric chloride (0.1 to .25 mole per mole of amine) is added. The stirred reaction mixture is allowed to warm until the evolution of nitrogen begins. This temperature varies with the types of reactants employed.(28,29, 33, 34). Sometimes it is necessary to raise the temperature to 40 or 50 degrees to bring about complete evolution of nitrogen, but most reactions can be carried out at room temperature or slightly lower. After the reaction is complete, volatile side products (and acetone) are removed by steam distillation. The side products include chloroacetone, chlorobenzene, and polymeric materials.

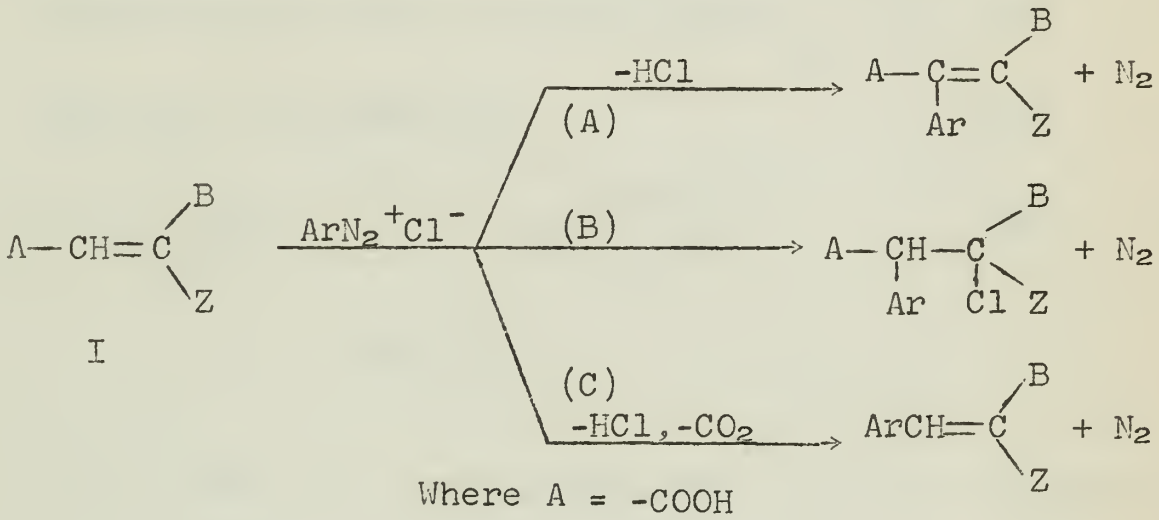
Diazonium salts with electron withdrawing groups in the <u>para</u> or <u>meta</u> positions give much better yields than the corresponding unsubstituted diazonium salts (2). Halide ions also enhance the rate (5, 6) and the yield (50) of the reaction. If a diazonium sulfate and copper sulfate are used instead of the diazonium chloride and copper chloride, no nitrogen is evolved until HCl is added (5). It has been shown, however, that the reaction can be forced to occur without halide ions if the temperature is raised sufficiently (50).

Since the optimum pH, solvent, chloride ion concentration and temperature depend on the kinds of reactants employed, yields have sometimes been improved by adjusting these variables (7). Rondestvedt has determined the effect of pH on the reaction of p-nitrobenzediazonium chloride with coumarin. He found an optimum pH of 2-4. At too high pH the formation of resins lowered the yield. At too low pH the Sandmeyer reaction took precedence.

The Meerwein reaction has the disadvantage that yields are usually low (20-40%), but the easy access which it affords to compounds which would be very difficult to synthesize by an alternat route often compensates for the low yields obtained.

C. SCOPE OF THE REACTION

In general, a Meerwein reaction may proceed to give one or more of the three alternative types of products, (see below). The unsaturated compounds which have been arylated by the Meerwein reaction may be represented by the general formula I below. (Formula I represents a trisubstituted ethylene, but there is no reason to assume that a tetrasubstituted ethylene would not also work.)



Where A = -COOH

(Z) is the group which directs the incoming aryl group to the β-position with respect to (Z). The relative powers of direction ar in the order of phenyl > vinyl > carbonyl or nitrile > methyl. The relative powers of direction among the carbonyl and nitrile groups have not been determined but it was shown that the benzoyl group is more effective than the carbalkoxyl group (8).

Mixtures of products arising from more than one of the alternative reactions are frequently observed (50, 1). Ordinarily decarboxylation occurs when maleic acid is arylated at pH of 3-5 (9), but at a pH of 2, type A product is produced without decarboxylation (10). The chloride ion concentration may also be a factor (1). In the course of working up the reaction, it is possible that type B products may be converted to type A or type C products by dehydrohalogenation or decarboxylative dehydrohalogenation (8, 9, 11-14). The biggest factor in determining which course the reaction will take is the nature of the olefin. Tables I, II and III give some of the typical Meerwein reactions:

Table I

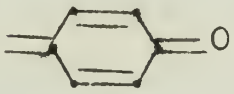
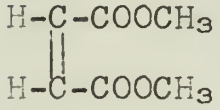
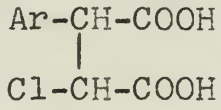
Reaction of type A:			Yield	Ref.
1)	I + ØCH=CH-CHO	$\longrightarrow$ ØCH=C(CHO)(Ar)	35%	4
2)	I + ØCH=CH-CN	$\longrightarrow$ ØCH=C(CN)(Ar)	76.5%	4
3)	I + CH_2=CH-COOH	$\longrightarrow$ ArCH=CH-COOH	60%	11
4)	I + CH_2=CH-CH_2COOH	$\longrightarrow$ ArCH=CH-CH_2COOH	5%	15
5)	III + ØCH=CH-CH=CH-$COOCH_3$	$\longrightarrow$ ØCH=CH-CH=C($COOCH_3$)(Ar)	19%	16
6)	III + ØCH=CH_2	$\longrightarrow$ ØCH=CH-Ar	23%	17
7)	III + 	$\longrightarrow$ 	68%	3

Table II

Reactions of type B:

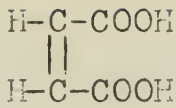
8)	III + CH_2=CH-C≡CH	$\longrightarrow$ $ArCH_2$-CHCl-C≡CH	40-45%	18
9)	II + CH_2=CH-CH=CH_2	$\longrightarrow$ $ArCH_2$-CH=CH-CH_2Cl	86.6%	19
10)	I + Ø-CH=CH-$COOCH_3$	$\longrightarrow$ Ø-CHCl-CH($COOCH_3$)(Ar)	30%	4
11)	I + 	$\xrightarrow{\text{hyd.}}$ 	47%*	4
12)	II + CH_2=CH-CN	$\longrightarrow$ $ArCH_2$-CHCl-CN	91%	20
13)	I + CH_3CH=CH-COOEt	$\longrightarrow$ Ar-$CHCH_3$-CHCl-COOEt	34%	16

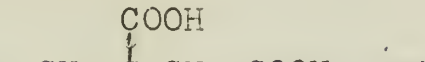
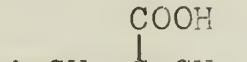
*Combined yield of mixed stereoisomers.

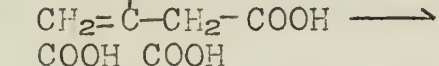
Table III

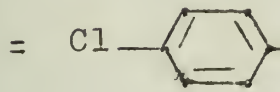
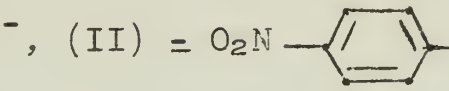
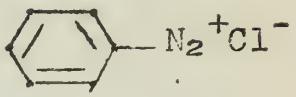
Reactions of type C:

14)	 + Ø-CH=CH-COOH	$\longrightarrow$ Ø-CH=CH-Ar	78%	4
15)	III + Ø-CH=CH-CH=CH-COOH	$\longrightarrow$ ØCH=CH-CH=CH-Ar	28%	16

16) II +  → ArCH=CH-COOH 58% 1

17) II +  →  — 1

18) II +  → ArCH=C-CH$_2$COOH — 1

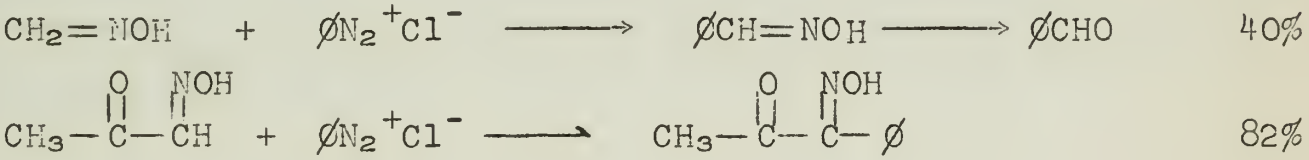
(I) =  , (II) =  , (III) = 

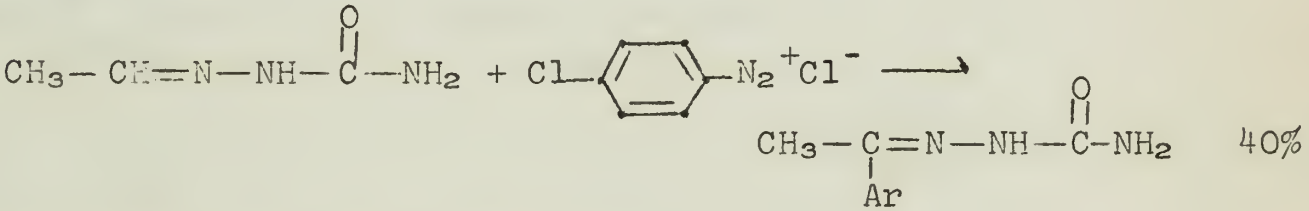
Ethylene and acetylene have been reported to be arylated by diazonium salts (5), but these results have not been duplicated (50).

A large majority of the known examples of the Meerwein reaction are listed by Rondestvedt (50).

Reactions for the arylation of oximes (21, 23), oximinoketones (21, 24), and semicarbazones (21) by diazonium salts have been reported. The reactions bear a close resemblance to the Meerwein reaction and perhaps ought to be included in the same category.

Examples of these three types are given below.





D. MECHANISM OF THE MEERWEIN REACTION

The mechanism of the Meerwein reaction is not too well understood at the present time. Most of the research in this field has not been aimed toward elucidating the nature of the mechanism but rather toward synthetic applications.

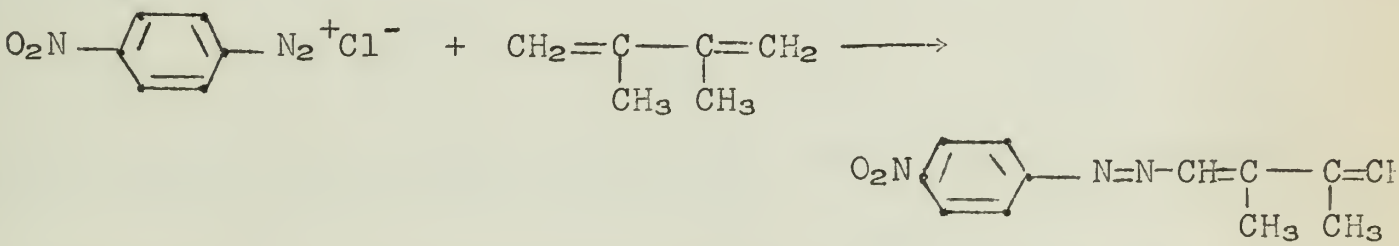
There are essentially two main theories as to the mechanism. One theory is that the attacking aryl group is a positive ion; the other is that it is a free radical.

The ionic mechanism as first proposed by Meerwein (4) and later supported by others (15, 17, 20, 25-27, 30) is that the diazonium

salt decomposes in the polar aqueous acetone solution to give phenyl carbonium ion, nitrogen gas, and chloride ion under the catalytic influence of $CuCl_2$. The phenyl carbonium ion would then attack the unsaturated compound to produce a second carbonium ion intermediate, which would then lead to the various types of products observed.

If one assumes that the carbonium ion produced is the more stab: of the two possibilities, then it follows that arylation will take place in the α-position of the α,β-unsaturated carbonyl compounds. If the aryl group were to attack the β-position, a carbonium ion would be produced adjacent to a carbonyl group. This arrangement would be thermodynamically unfavored. On the basis of the above arguments Meerwein made incorrect structure assignments to two compounds which he prepared, β-(p-chlorophenyl)-α-chlorobutyric acid and methyl β-(p-nitrophenyl)-α-chlorobutyrate, by arylating crotonic acid and its ester. He assumed the compounds to be α-(p-chlorophenyl)-β-chlorobutyric acid and methyl α-(p-nitrophenyl)-β-chlorobutyrate respectively. Koelsch repeated the reactions and determined the correct structures (16).

Since the rate of nitrogen evolution is very dependent on the nature of the unsaturated compound (16), an intermediate complex between the nitrogen-containing compound, $CuCl_2$ and the unsaturated compound is indicated, although it has not been demonstrated. Speculations about the nature of such a termolecular intermediate have been made (31). Brunner (17), in the study of the reaction of 1,1-diphenylethylene with diazonium salts, noticed a dark red color at the beginning of the reaction before $CuCl_2$ was added to the reaction mixture. He attributed the initial color to the formation of an intermediate ion containing the azo group, which in the presence of Cu^{++} would be unstable and would split out N_2. If Cu^{++} were not present, the ion would lose a proton and the azo dye would form. The formation of azo dyes is observed in the absence of cupric salts (32, 35, 36).



Meerwein argues against this type of intermediate on the basis that compounds of the type

show little tendency to split out N_2 spontaneously (4). The question remains as to whether the above types of compounds will split out N_2 in the presence of cupric salts.

Koelsch (16, 37) has postulated a free radical mechanism on the basis of several observations. Acetone, which is used as a solvent in the reaction, becomes chlorinated in the process of the reaction. This would indicate the presence of free radicals (38). The formation of chloroacetone might be explained by the following sequence:

$$R. + CH_3CCH_3 \longrightarrow RH + CH_3-\overset{O}{\overset{\|}{C}}-CH_2. \xrightarrow{[Cl.]} CH_3\overset{O}{\overset{\|}{C}}-CH_2Cl$$

Conditions which promote good yields in the Meerwein reaction (i.e., use of $CuCl_2$, dilute HCl, NaOAc, diazonium salts with electron withdrawing substituents on the ring, etc.) are the same conditions which promote good yields of chloroacetone when the unsaturated compound is not present (4).

The catalytic effect of sodium acetate could be explained by the fact that diazonium acetates decompose more readily into free radicals than do the corresponding diazonium chlorides (39). Koelsch's proposed mechanism is as follows:

a) $\phi\overset{\oplus}{N}\equiv N + CH_3COO^- \rightleftharpoons \phi-N=N-O-\overset{O}{\overset{\|}{C}}-CH_3$

b) $\phi-N=N-O-\overset{O}{\overset{\|}{C}}-CH_3 \longrightarrow \phi. + N_2 + CH_3COO.$

c) $\phi. + RCH=CHR' \longrightarrow R\dot{C}H-CH(R')(\phi)$

The aryl radical attacks in such a way so as to produce the more stable free radical. The observed differences in the point of attack of the aryl group are in agreement with the fact that the relative powers of adjacent groups to stabilize free radicals are in the order of

$$\phi\rangle \quad \rangle C=C\langle \quad \rangle -\overset{O}{\overset{\|}{C}}- \quad \text{or} \quad -CN\rangle \quad -CH_3 \qquad (40).$$

Thus crotonic acid and acrylic acid are arylated in the β-position rather than in the α-position.

d) $R-\dot{C}H-CH(R')(\phi) + Cu^{++} \longrightarrow R-\overset{\oplus}{C}H-CH(R')(\phi) \longrightarrow$ etc.

e) $Cu^+ + .OAc \longrightarrow Cu^{++} + OAc^-$

Koelsch's sequence explains the observed orientation of the aryl group in the products but it does not explain the fact that halide ion is necessary for the reaction to occur or that the rate of nitrogen evolution is dependent upon the compound being arylated and

upon the presence of Cu^{++}. Furthermore, whenever the carbonium ion intermediate has its positive charge on a carbon adjacent to a carbonyl or cyano group, one would expect rearrangements to occur to stabilize the carbonium ion. Such rearrangements have not been observed.

Kochi has shown that the Meerwein reaction will proceed much faster if cuprous chloride is used instead of cupric chloride (41). He obtained a 75% yield of α,4'-dichlorobibenzyl from p-chlorobenzenediazonium chloride and styrene. As catalyst, .05 mole of cuprous chloride per mole of amine was employed. The reaction was carried out at 0° in a deoxygenated system, since oxygen inhibits the reaction. Quantitative evolution of nitrogen was obtained in a short period of reaction time. On the other hand, Brunner (17), carried out a reaction employing the same reactants but the catalyst was .2 mole of $CuCl_2$ per mole of amine. In order to bring about complete evolution of nitrogen the reaction mixture was heated for 12 hours at 35-40°. A 32% yield of p-chlorostilbene was obtained.

Kochi postulates that the reason that cupric ion is effective at all is because it can easily be converted to cuprous ion by the following reaction (41, 42).

$$Cl^- + 2CuCl_2 + CH_3COCH_3 \longrightarrow 2CuCl_2^- + H^+ + CH_3COCH_2Cl$$

This reaction could explain the fact that acetone promotes the Meerwein reaction.

On the basis of Kochi's findings, Dickerman has postulated a free radical mechanism involving Cu(I) as the catalyst for the homolysis of the diazonium salt (43).

a) $ArN_2Cl + CuCl_2^- \longrightarrow ArN_2\cdot + CuCl_3^-$

b) $ArN_2\cdot \longrightarrow Ar\cdot + N_2$

c) $Ar\cdot + \diagup C{=}C\diagdown \longrightarrow Ar{-}\overset{|}{C}{-}\overset{|}{C}\cdot$

d) $Ar{-}\overset{|}{C}{-}\overset{|}{C}\cdot \xrightarrow{CuCl_2} Ar{-}\overset{|}{C}{-}\overset{|}{C}{-}Cl + CuCl$

e) $Ar\cdot + CuCl_2 \longrightarrow ArCl + CuCl$ (Sandmeyer)

Cu(II) serves both as a radical trap and chain transfer agent. It is interesting to note that polymerization of acrylonitrile can be brought about by use of cuprous ion in an unbuffered solution of p-nitrobenzenediazonium salts, acrylonitrile and dilute HCl (44). Presumably there is no Cu(II) to serve as chain transfer agent, so polymerization occurs.

On the other hand, polymerization of readily polymerizable substances such as acrylonitrile can be prevented by cupric chloride (45, 1). Instead of polymerization, addition to the double bond occurs.

$$Ar. + CH_2{=}CH{-}R \longrightarrow ArCH_2{-}\dot{C}H{-}R$$

$$ArCH_2{-}\dot{C}H{-}R + CuCl_2 \longrightarrow ArCH_2{-}CHCl{-}R + CuCl$$

Where R= —CN or —Ø

The yields of styrene addition products were 54 to 78% when the sources of free radicals were phenyl azotriphenylmethane, benzoyl peroxide, N-nitroso-p-nitroacetonilide and p-nitrobenzenediazonium chloride.

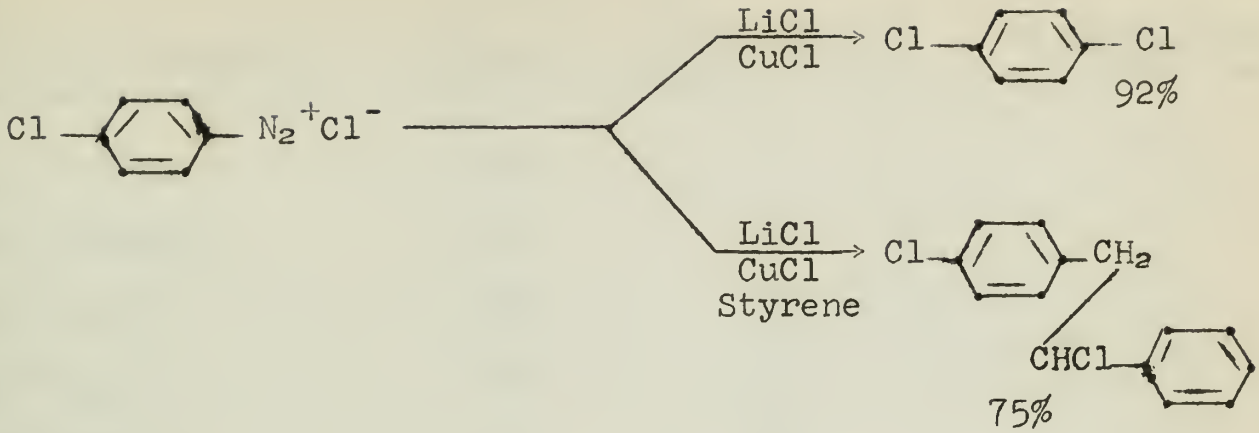
In support of a mechanism such as Dickerman's, a kinetic study has revealed that the rate of evolution of nitrogen is first order in diazonium ion and in Cu(I).

$$\frac{d(N_2)}{dt} = k(ArN_2^+)\ [Cu(I)] \qquad (1, 6)$$

The rate of nitrogen was also found to be a complex function of Cl^-, Cu(II) and olefin concentrations. Increasing olefin concentrations increased $\frac{dN_2}{dt}$ and the yield of Meerwein product up to plateau values, where further increases in olefin concentration did not increase the rate or yield. Increasing Cu(II) concentrations caused a greater rate of nitrogen evolution but decreasing yields of Meerwein product, whereas the yield of Sandmeyer product increased Increasing chloride concentrations caused a decrease in the yield of Meerwein product. In view of the fact that in the absence of copper salts or halide ions the reaction goes poorly or not at all, a more detailed mechanism must be proposed to explain all of the observations.

A complication in the study of the kinetics is the multitude of equilibria which exist between Cu(I), Cu(II) and Cl^-. It is not possible to assign to any particular species a role in the mechanism without further study of the reaction kinetics. Although the complex anion, $CuCl_2^-$, has tentatively been assigned the catalytic role, some other species of Cu(I) may be the true catalyst.

The Sandmeyer reaction and the Meerwein reaction are analogous, since both involve aryl free radicals (1). How effectively the Meerwein reaction competes with the Sandmeyer reaction has been determined in the reaction of p-chlorobenzenediazonium chloride with styrene (41).



In the absence of styrene, p-chlorobenzenediazonium chloride was converted in 92% yield to p-dichlorobenzene. With styrene added the reaction yielded 75% of α-4'-dichlorobibenzyl.

E. DECARBOXYLATION MECHANISM

The decarboxylation step was visualized by both Meerwein and Koelsch to proceed by way of a carbonium ion intermediate. Meerwein postulated that decarboxylation occurred after formation of a β-lactone. This has been shown to be unlikely (46). At the pH of the reaction it is also unlikely that decarboxylative dehydrohalogenation would occur (12, 46). A concerted mechanism whereby CO_2 and H^+ would be removed in one step was also proposed (47). In keeping with a completely free-radical mechanism a concerted mechanism involving Cu(II) can be postulated.

A more detailed study of the decarboxylation mechanism must be made before any definite conclusions can be made.

F. STEREOISOMERIC STUDIES

Although trans products are often obtained in the Meerwein reaction (14, 25, 26, 48), in some cases mixtures of cis and trans isomers were obtained (12,13,17,31,49). Both the cis and the trans isomers of β-(p-bromophenyl)cinnamic acid reacted with p-nitrobenzenediazonium chloride to yield only one isomer of α-(p-bromophenyl)-β-(p-nitrophenyl)-styrene (26).

Table (IV) summarizes the results obtained by Rondestvedt in the arylation of cis and trans isomers by p-nitrobenzenediazonium-chloride (31).

Table IV

Unsaturated Compound	Yield	% *cis*-isomer	% *trans*-isomer
Methyl maleate	26%	24	66
Methyl fumarate	48%	29	55
Butyl maleate	40%	32	62
Butyl fumarate	62%	31	58
Maleonitrile	45%	33	57
Fumaronitrile	52%	30	62

The crude reaction mixture was treated with collidine to convert any addition products to olefins. Although in each case, the overall yield of mixed isomers was greater when the original olefin was *trans*, the ratio of *trans* to *cis* olefin was roughly 2:1. This was taken as evidence for the existence of a common intermediat preceding both isomers. To determine whether isomerization could have occurred following reaction, *p*-chlorophenylmaleonitrile was treated under Meerwein conditions and was recovered unchanged. Although the above evidence does not conclusively prove the existance of a common intermediate, it is the best available at present.

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CHARGE TRANSFER COMPLEXES

Reported by R. J. Tuite December 12, 1957

INTRODUCTION

Charge transfer complexes, or molecular addition compounds, are a class of weakly bonded compounds in which there is stabilization due to the transfer of charge. Although any molecule could be called a charge transfer compound, this discussion will be limited to the true complexes, i.e. those compounds which must be described in terms of a weak, non-classical bond, such as the picrates and the brown (as opposed to violet) solutions of iodine. In this seminar, an attempt will be made to illustrate the wide variety within this class of compounds, to mention some of the current research being carried out in this field, and finally, to discuss some of the theoretical considerations of Mulliken, Bayliss, and Orgel. Only the 1:1 non-radical complexes are included. Crystal structure and biological applications will not be discussed.

The subject has been reviewed recently by Andrews (1), Orgel (2), and Terenin (3). The iodine complexes have also been covered separately (4). The present seminar will be limited to work which has been done since these reviews and will refer to them only for the sake of completeness.

Several theories (1) have been proposed to account for the existence of the molecular addition compounds, since they do not follow the classical rules of valence saturation. Dewar (5) first suggested the term "pi-complex". Brackman (6) proposed that the complex bond could be described as a resonance hybrid of a no-bond and a bonded structure. Mulliken (7) further developed this hypothesis in terms of the Lewis concept of acids and bases, i.e. electron donor-acceptor interaction. He gives a quantum mechanical treatment of the complexes in terms of two structures.

$$D\ A \longleftrightarrow D^{+}A^{-}$$

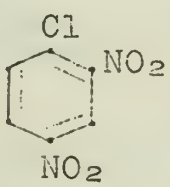
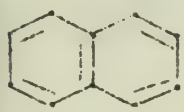
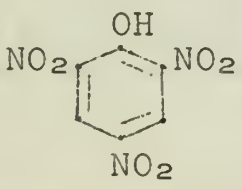
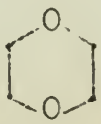
where D is the donor and A the acceptor. Mulliken's treatment will be covered later in this seminar.

The term "charge transfer complex" arises from the well-known charge transfer band in the ultraviolet spectrum of many compounds. This band corresponds to an electronic transition between two structures differing in their charge distribution. For example, in the spectrum of p-nitrophenol there is a maximum at 286 mμ (8), which is assigned to the transition

There is a similar band in the spectra of these complexes which is not present in the original reactants. For this reason, Mulliken has named them "charge transfer" (C.T.) complexes.

GENERAL SURVEY

Even in the limited sense used here, there are a large number of possible C.T. complexes. When a given donor interacts with a given acceptor, a complex is in general formed. Some of the common donor species are: ROH, RSH, R_2O, aromatic hydrocarbons, $Ar(Y)_n$ (where Y is an electron-repelling group), RNH_2, RX, halides and other anions, olefins, and to some extent even the saturated hydrocarbons, notably cyclopropane. When in a complex, all these substances have the ability to stabilize the induced positive charge. Some of the common acceptor species are X_2 (the halogens and interhalogens), electron deficient olefins (e.g. quinones and maleic anhydride), H^+, Ag^+, several other cations, $Ar(Z)_n$ or RZ (where Z is an electron-withdrawing group), and even molecular oxygen. In contrast to donors, the acceptor species are electrophilic. A few examples of C.T. complexes and some thermodynamic data are listed below.

DONOR	ACCEPTOR	Keq (l/mole)	$\triangle H^\circ$ (kcal/mole)	$\triangle F^\circ$ (kcal/mole)	$\triangle S^\circ$ (cal/mole degree)	REF.
		0.45	-13.1	+0.47	-45.8	9
	I_2	1250	- 7.8	-3.3	-15.5	10
t-BuOH	I_2	11.1	- 1.43	-3.4	- 6.7	11
	I_2	0.013	---	---	---	12
		2.31	- 3.1	-0.67	- 8.7	13
	I_2	9.1	- 3.30	-1.31	- 6.7	11 14

The data included in the table were obtained from measurements on solutions of the complexes in "inert" solvents at temperatures ranging from 23° to 27°. K_{eq} is obtained spectroscopically as will be described later, $\triangle H^{\circ}$ from a plot of ln K_{eq} vs. 1/T, $\triangle F^{\circ}$ by $\triangle F^{\circ} = -RT \ln K_{eq}$, and $\triangle S^{\circ}$ from $\triangle H^{\circ} = \triangle F^{\circ} + T\triangle S^{\circ}$. Not all investigators are in agreement at this time as to the correct values for these quantities, but the table will serve to give semi-quantitative estimates. K_{eq} values usually range from about 10^3 for the very strong complexes to essentially zero for the very weak hydrocarbon I_2 complexes. Values of $\triangle H^{\circ}$ are generally in the range -0.5 to -4.0 kcal./mole, although some of the stronger complexes have much larger negative heats. A number of similar measurements were made by other investigators (15).

It will be of value at this time to arrange donors and acceptors according to the Mulliken classification (7).

Symbol	Name	Description and/or examples
		DONORS
n	onium	unshared electron pair of O, S, N
bπ	pi	highest energy electron pair of π M.O.
bσ	sigma	RI, RCO_2R' (complex usually unstable)
R	Radical	easily ionized odd electron system
		ACCEPTORS
v	vacant orbital	BF_3, $AlCl_3$, metal salts
π	pi	electronically deficient π M.O.
σ	sigma	halogens, H-acids
Q	Radical	odd electron system with high electron affinity

A more complete classification can be found in reference (7), in which Mulliken further divides these general classes into subclasses, thereby providing a systematic classification of all C.T. complexes. Numerous examples are also included.

RECENT RESEARCH WORK

Interest in this field was stimulated by Benesi and Hildebrand (16), who successfully demonstrated the existence of a 1:1 complex between benzene and I_2 by varying the concentration of both components in an inert solvent. They derived the following expression, which can be solved graphically for K_{eq}.

$$[I_2]\frac{\ell}{A} = \frac{1}{K_{eq}\epsilon_c}\frac{1}{[Bz]} + \frac{1}{\epsilon_c}$$

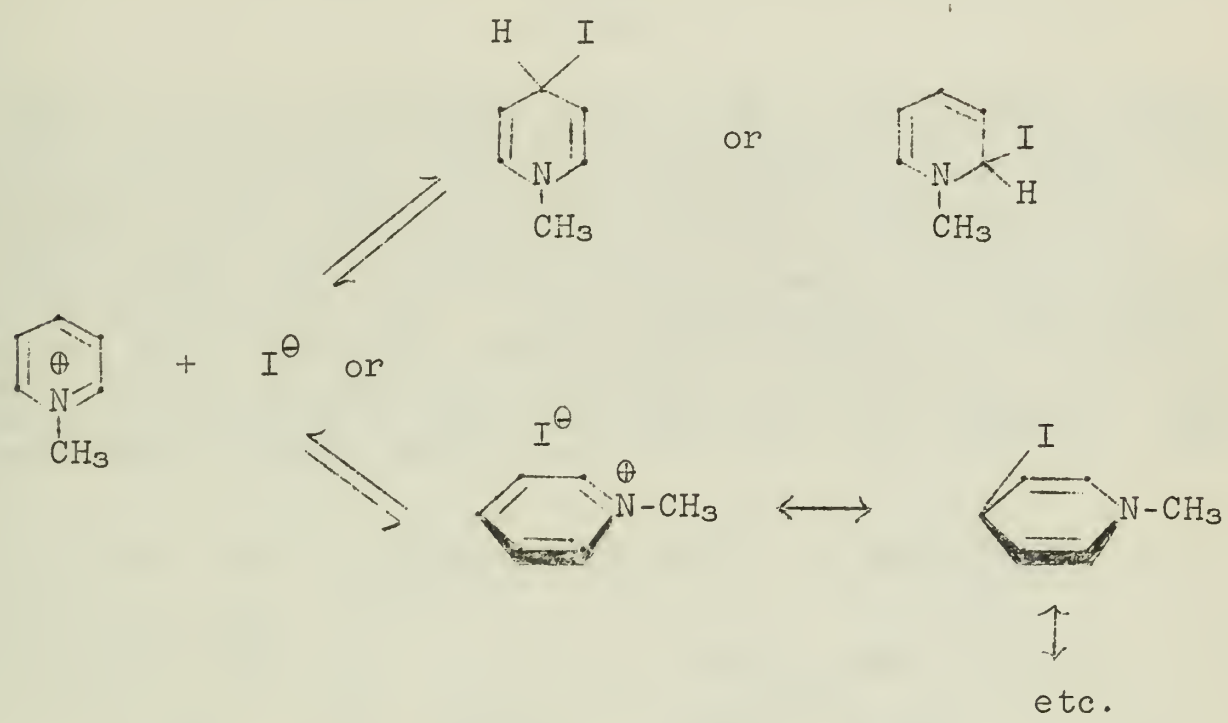
ϵ_c is the molar extinction coefficient of the C.T. band of the complex,

A is the absorbancy,

ℓ is the path length in cm.

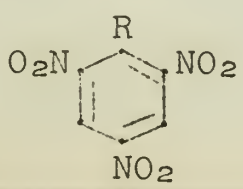
Using this equation, they calculated K_{eq} values for a number of aromatic substances complexed with iodine. Other authors (17) have used similar methods to determine K_{eq} values. All these relations assume the formation of only one complex.

Kosower and Klinedinst have studied a series of substituted pyridinium salts and have demonstrated the presence of a C.T. complex (18). Due to the fact that aqueous solutions of 1-methylpyridinium iodide do not obey Beer's Law for a specific band in the U.V., they suggested that the ionized salt was in equilibrium with another substance which could be either of two structural types, a σ- type addition compound or a π-complex.



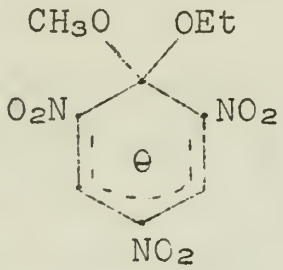
Brown and Brady (19) have shown that the σ-complexes and π-complexes can be distinguished by the effect of methyl substitution on K_{eq}. For example, the HCl π-complex with 1,2,3,5-tetramethylbenzene has a K_{eq} 1.82 times as great as with toluene, while the $HF\text{-}BF_3$ σ-complex with 1,2,3,5-tetramethylbenzene has a K_{eq} 5.6×10^5 times as large as with toluene. Using this principle, Kosower and co-workers (18b,20) prepared several methyl substituted 1-methylpyridinium iodides and found that the K_{eq} values varied only slightly. For example 1,2,4,6-tetramethylpyridinium iodide had a K_{eq} of 1.8 as compared with a K_{eq} of 2.3 for the 1-methyl compound. On this basis, they concluded that a π-type complex was present.

Ainscough and Caldin have studied the mechanism of nucleophilic attack on certain 1-substituted 2,4,6-trinitrobenzenes by ethoxide ion in ethanol (21).



R = OCH_3 trinitroanisole (TNA)
= H trinitrobenzene (TNB)
= CH_3 trinitrotoluene (TNT)

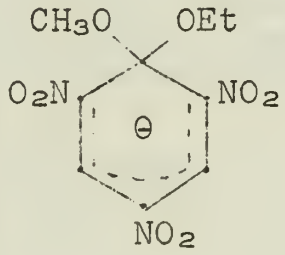
When R = OCH_3, the reaction proceeds rapidly at room temperature to an intermediate whose ultraviolet and visible spectra were identical to those of the intermediate formed when 2,4,6-trinitrophenetole reacts with methoxide ion in methanol. The sodium salt of the intermediate was also isolated. The structure of the anion is believed to be



However at 0°, an initial rapid rise in the optical density of the reaction mixture followed by a leveling off to a slow steady increase indicates there are two intermediates being formed, one a product of a "fast" reaction, and the other (presumably the addition product above), a product of a "slow" reaction. At -70°, the rate of the "fast" reaction was measured and found to be first order in both TNA and OEt^-. Acid decolorization of the product is general acid catalysed, whereas decolorization of the second addition product is specific hydronium ion catalysed. The product of the first reaction is best described as a C.T. complex. They proposed the following mechanism.

1. $TNA + OEt^- \underset{}{\overset{\text{fast}}{\rightleftharpoons}} [TNA \cdot OEt^- \longleftrightarrow TNA^- \cdot OEt]$

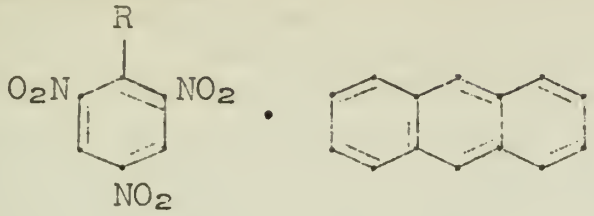
2. $\left.\begin{matrix} TNA + OEt^- \\ \text{or} \\ (TNA \cdot OEt)^- \end{matrix}\right\} \xrightarrow{\text{slow}}$



The authors attempted to distinguish between the latter two possibilities by using the rate and equilibrium data to calculate the entropies of activation ($\triangle S^{\ddagger}$). This distinction is impossible, however, since $\triangle S^{\ddagger}$ is path independent and therefore does not depend on how the transition state was formed. Furthermore the transition states for the two possible reactions are probably identical.

The steric requirements for complex formation are relatively unimportant in some instances, since the distance separating the components of a complex is but slightly less than the sum of their van der Waals' radii (1). Examples are the aromatic iodine complexes. However, as might be expected, steric requirements do play an important role in many cases, for example the picrates and related compounds. Ross and co-workers (22), in attempting to correlate the Hammett σ- values with complex stability, studied

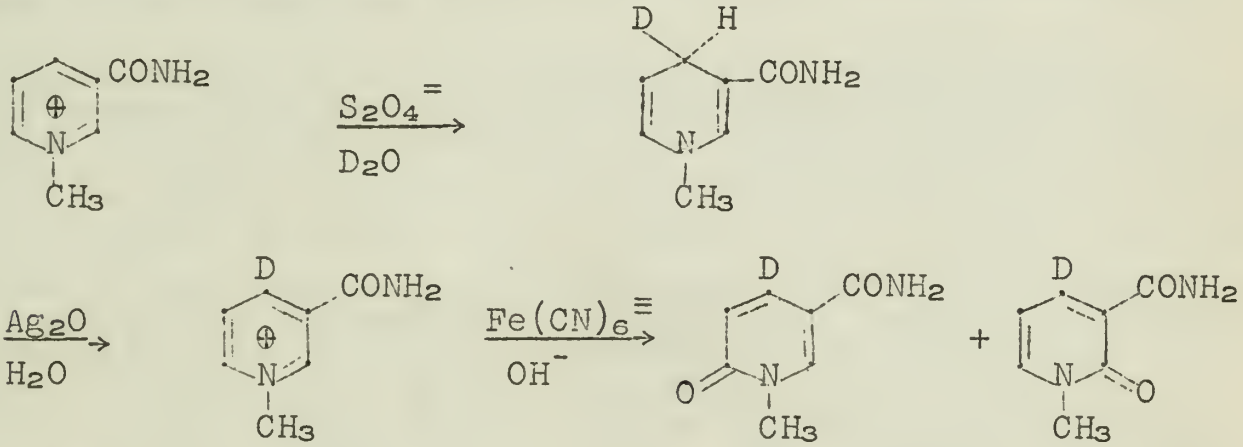
a series of 1-substituted 2,4,6-trinitrobenzene·anthracene complexes in chloroform.



R=H, CH_3, OH, OCH_3, Cl, I

Since the R group would be pushed somewhat out of the plane of the ring by the o-NO_2 groups, they expected a good correlation between K_{eq} and the inductive effect of R. They found however, that the value of K_{eq} depended on the size of the substituent. That is, K_{eq} decreases in the order R=H>OH>OCH_3>CH_3>Cl>I rather than in the expected order Cl>I>OCH_3>OH>H>CH_3, as arrived at by the ionization constants of the α-substituted acetic acids. Although the amount of resonance interaction also varies due to the different sizes of the groups, the general trend seems to indicate a simple steric requirement. Castro and Andrews (41) have found that, due to the fact that coplanarity is prevented when ortho substituents are introduced in biphenyl, K_{eq} values for its TNB complex decrease with increasing ortho substitution.

Kosower (23) has attempted to correlate the reactive position of some 1-substituted pyridinium salts with the ability of the salt to complex. Those salts in which the cation and anion are suitable for complex formation are attacked in the 4-position; those in which a complex is unlikely are attacked in the 2-position. In the examples given, however, there are too many parameters varying at the same time. Notably, many of his examples involve complex biochemical reactions in which the stereochemical requirements are probably specified by other forces. The following scheme (24) will illustrate the general trend that Kosower observed.



In the reduction, $S_2O_4^{=}$, a relatively good complexing agent as shown by its electrode potential, promotes attack at the 4-position. In the oxidation, OH^-, a notoriously poor complexing agent, attacks at the 2-position. This type of correlation may prove useful as a synthetic tool, but no direct application has yet been made.

Since the excited state of a C.T. complex is dipolar in nature, solvent polarization is often an important factor to be considered. By adding specified amounts of $LiClO_4$, Kosower (20) showed that the frequency of C.T. absorption for aqueous solutions of some

methyl substituted pyridinium salts is lowered by increasing the dielectric constant of the solvent. This is explained by the increased stabilization of the dipolar excited state which results in a lowering of the transition energy. Ross (25) has demonstrated the variance of K_{eq} of some b//·π complexes with changing concentration of Et_3N. Perhaps the most graphic example of solvent stabilization versus destabilization is the varying degree of solvation of 1-pyridinium cyclopentadienylide in different solvents (26, 18b).

Solvent	Color of solution
aqueous acid	colorless (protonation)
aqueous base	yellow
ethanol	orange
acetone or chloroform	red
benzene or ether	reddish-purple
petroleum ether	bluish-purple

Kosower proposes a progressively destabilized ionic ground state with respect to an "uncharged" excited state, the contributing structures being for both states

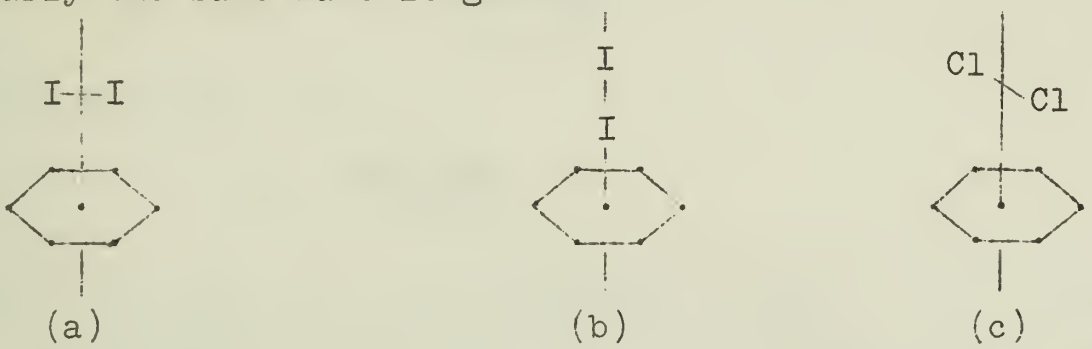
There are numerous examples of radical·radical C.T. complexes in the recent literature (27), but they are mentioned here only for the sake of completeness.

The equation of Benesi and Hildebrand and its various modifications have been inadequate in certain instances. For example, it has been found that, while theory predicts that both K_{eq} and ϵ_c should increase with increasing methylation of the ring in the benzene·I_2 series, K_{eq} increases but ϵ_c actually decreases. In view of this and other discrepancies, Murakami (28) suggested the existence of "orientation isomers", i.e. isomeric complexes differing only in the relative orientation of the acceptor with respect to the donor. He also maintained that the oscillator strength is the proper measure of the intensity of a transition, and it should be used in place of ϵ_c. The oscillator strength "f" is defined as

$$f = \frac{mc^2}{N\pi e^2} \cdot \frac{10^3}{\log_{10} e} \int \epsilon(\nu) d\nu = 4.32 \times 10^{-9} \epsilon_c \Delta\nu$$

Orientation has always been a problem in quantitative calculations. Infrared analysis provides a possible method for distinguishing between the b//.π and n.π picrate complexes (42) due to differences in the asymmetric vibration of the N-O bond. Whereas the b//-π complexes (e.g. aryl picrates) have only one

band in this region, the n.π complexes (e.g. amine picrates) exhibit two distinct bands of nearly equal intensity. This is explained as due to one nitro group of the picric acid interacting preferentially with the amine function of the donor. The authors suggest that both types could exist with the same donor-acceptor pair. Mulliken (7) suggested a flat orientation (a) for the benzene·I_2 complex. More recent IR studies (29), however, seem to indicate an axial isomer (b), and in some cases, like benzene·Cl_2 (30), an oblique orientation (c). There is a possibility that more than one of these isomers are present in the same medium, and yet are undetectable by spectroscopic means because the C.T. bands occur at nearly the same wave length.



(a) (b) (c)

DeMaine (31) first succeeded in demonstrating the existence of two distinct structural isomers in a single complexing system. In the ground state of benzene, the lowest ionization potential is twofold degenerate, i.e. there are two electrons with the same ease of removal. In anisole, however, and in some other methoxy substituted benzenes and biphenyls, these energy levels are split by an amount sufficient to give rise to two distinct bands in the spectra of their complexes with iodine. These bands occur at 345 and 295 mμ in anisole·I_2.

THEORETICAL CONSIDERATIONS AND RELATED PROBLEMS

Due to its consistency with experimental results, the Mulliken Theory is the most universally accepted description of these complexes (32,7). Mulliken treats the interaction between the donor D and the acceptor A by the Valence Bond method, using the no-bond and dative structures as principal contributing structures. The ground state is denoted by

$$\Psi_N = a\psi_0(D,A) + b\psi_1(D^+A^-) \quad a \gg b$$

That is, in the ground state, there is a predominance of the no-bond structure, with a small (b^2/a^2) but significant contribution of the dative structure. The excited state is denoted by

$$\Psi_E = a^*\psi_1(D^+A^-) - b^*\psi_0(D,A) \quad a^* \gg b^* \quad a^* \approx a;\ b^* \approx b$$

That is, in the excited state, there is a predominance of the dative structure. Additional terms are required for accurate quantitative results, but these two terms illustrate the C.T. theory. The important concept here is that both the ground state and the excited state of the complex are definite 1:1 compounds, and that the energy of transition is not a function of the two individual components, but is characteristic of the complex as a whole.

The various parameters arising in the Mulliken Theory can be obtained by the usual semi-empirical methods. Normalization of the ground state wave function gives the relation

$$a^2 + 2abS + b^2 = 1$$

where S is the overlap integral and can be calculated assuming the geometry of the molecule. Another expression involving both a and b can be obtained by a consideration of the energy relationships. A second order perturbation is required, giving for the energy

$$E_N = E_o - \frac{(H_{o1}-E_oS)^2}{(E_1-E_o)} + ...$$

and for the ratio b/a

$$\frac{b}{a} \approx - \frac{H_{o1}-E_oS}{E_1-E_o}$$

where E_o is the sum of the energies of D and A taken separately, modified to include non-C.T. forces,
E_1 is a similar term for D^+-A^-, but also includes ionic interaction,
H_{o1} is an energy function describing interaction of both resonance structures.

From a similar calculation, the values of a* and b* are obtained. Therefore we have a method of estimating relative structural contributions in both states. The energy difference $(E_E - E_N)$ is related to the frequency of C.T. absorption by $\Delta E = h\nu$. The oscillator strength for this transition can then be obtained from dipole moment calculations.

Application of the theory presupposes certain symmetry requirements. To effect interaction, the donor electron and empty acceptor orbital must be of the same spin species, or in the heavier atoms like iodine, of the same spin-orbital species. This is equivalent to saying that the electrons must be paired. A former second requirement - that the components D and A both be closed-shell ions or molecules in the singlet state - has been modified to include radical·radical interaction.

From the nature of the ground and excited states, it follows that the energy difference attending the transfer of an electron is a function of the ionization potential of the donor I_D, and the electron affinity of the acceptor E_A (12). The quantities of actual importance are their components in the direction of C.T. interaction. This can be represented by the following equation:

$$\Delta E = h\nu = I_D - E_A + W$$

where W, the stabilization energy due to the interaction, can be represented by:

$$W = \frac{2\beta^2}{I_D-E_A} \qquad \text{where } \beta \text{ is a constant}$$

It should be noted that a low I_D and a high E_A favor a stable complex. In order of magnitude, $I_D - E_A$ is the most significant part of this expression. For this reason, a number of investigators have been able to obtain good straight line plots of I_D vs. $\lambda_{C.T.}$ in a series of complexes containing different donors but the same acceptor (33).

Substantial evidence for the truth of Mulliken's theory lies in the work of Nakamoto (34), who studied the complex between hexamethylbenzene and 1,3,5-trinitrobenzene as well as a number of other complexes of known crystal structure. Using radiation of the same frequency as C.T. absorption, he measured the relative intensities of absorption parallel to and perpendicular to the planes of the two rings. He found that the intensity of absorption perpendicular to the plane of the rings was greater than that parallel to the plane. This is in marked contrast to the result observed with ordinary aromatic molecules. However, this difference could be predicted by Mulliken's theory, since electron transport occurs between parallel rings and can be brought about only by a component of incident light oscillating perpendicular to the ring plane. Other substantiating evidence for the Mulliken theory is the constancy of the triplet→singlet transition spectra for these complexes (35).

It is now known that I_2 interacts with even the saturated hydrocarbons as is evidenced by the fact that I_2 exhibits in solution a band which is lacking in the vapor. Bayliss (36) explains this as merely a spectral shift due to physical perturbations within the solvent. According to him, this apparent shift is due to two effects, a cage effect and an effect due to the dielectric constant of the solvent. The solvent cage can hinder the vibrations of the solute molecule, thereby affecting also its energy of transition to the excited state. The dielectric constant of the medium is effective in stabilizing the excited solute molecule, thus lowering the energy required for transition. On the other hand, Orgel and Mulliken (37) interpret this phenomenon in terms of what they call "contact C.T. complexes". If the acceptor molecule is a closed-shell species, the donated electron must fill an anti-bonding orbital. For example, in the I_2 acceptor, the electronic states can be described as:

for I_2 ..... $\sigma^2\pi^4\pi^{*4}$

for I_2^- ..... $\sigma^2\pi^4\pi^{*4}\sigma^*$

* indicates an anti-bonding orbital

Since anti-bonding orbitals have contours farther removed from the internuclear bond, the electron acceptance radius may be larger than the van der Waals' radius. Since complex formation depends on orbital overlap, there will be a complex formed even before a potential donor molecule comes within van der Waals' distance of the acceptor molecule. Although most workers support either the Bayliss theory (38) or the Orgel-Mulliken theory (39), it seems likely that both approaches are equally good approximations.

By a purely statistical approach, Orgel and Mulliken (37b) have modified the C.T. theory to include the concepts of orientation isomerization and contact C.T. complexes. They replaced certain

lone terms by summation terms which take into account all the possible orientation isomers, and discovered that the observed K_{eq} was actually the sum of all the individual K's, whereas the observed ϵ_c was actually an average value of all the isomers.

$$K_{eq} = \Sigma_i K_i \qquad \epsilon_c = \frac{\Sigma_i K_i \epsilon_{c_i}}{\Sigma_i K_i}$$

This modification becomes important whenever there is a significant number of isomers present which do not have the same orientation as the predominant isomer. This could adequately explain the discrepancy in the methylated benzene·I_2 series if the stability of one of two possible orientation isomers is dependent on methyl substitution. This is substantiated by the fact that one of the isomers must be unsymmetrical.

DeMaine (40) discovered that $\triangle H_f$ values for the alcohol·I_2 complexes were independent of solvent polarity in moderately dilute solutions. He postulates that the highly H-bonding solvents interact intramolecularly to form an ordered liquid lattice, into which the I_2 molecules can fit without disrupting the lattice. As long as the number of I_2 molecules does not exceed the number of lattice holes, the $\triangle H$'s remain constant.

CONCLUSION

C.T. complexes are an interesting group of compounds from many points of view. To the structural chemist, they represent a non-classical type of bonding. Since they are probably intermediates in a number of reactions, as evidenced by color changes, they are of significance in the study of mechanisms. Finally, C.T. complexes are important to the synthetic organic chemist, since there is some indication that both reactivity and position of attack can be controlled by appropriate complexing.

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SULFENAMIDES

Reported by R. T. Hawkins December 16, 1957

In this seminar will be discussed mainly the preparation and properties of aliphatic sulfenamides. Sulfenamides, $RSNR_2$, may be considered to be the amides of the hypothetical sulfenic acids, RSOH. Sulfenamides possess a covalent sulfur-nitrogen linkage. The sulfur atom is divalent and the nitrogen is trivalent. For brevity in this report, linear formulae will be written $RSNR'_2$. It should be understood that R' may be H unless otherwise indicated. Two reviews on sulfenamides have appeared (1,4), the latest citing references up to ten years ago (1).

I. ALIPHATIC SULFENAMIDES

The first sulfenamide, a resonance-stabilized heterocycle, was reported by Busch in 1896 (5). Since that time, arylsulfenamides have become well known, and have even been advocated as derivatives in identifying amines and thiophenols (6). By contrast, the first completely aliphatic sulfenamide was not reported until 1939 by Rheinboldt and Motzkus (8). Earlier researchers, plagued by the instability of aliphatic sulfenamides, were unsuccessful in characterizing pure products (32). Investigations with alkylsulfenyl iodides led Rheinboldt and co-workers to treat t-butylsulfenyl iodide with several aliphatic amines. No reaction was observed between arylamines and t-butylsulfenyl iodide.

Low molecular weight sulfenamides in the aliphatic series are liquids. Some of the higher members of the series are crystalline solids. In contradistinction to the aromatic series, the aliphatic sulfenamides are noted for lesser stability. Aliphatic sulfenamides are scarce. For example, one review tabulates 166 sulfenamides, only three of which are completely aliphatic (4). Sulfenamides are often colorless, with an amine-like odor (4,8), when first distilled or crystallized. Decomposition (by a route not yet established in most cases) may occur over a period of weeks or even, in some cases, within a matter of a few hours (1,2,9). More will be said later about decomposition products.

A. Syntheses of Sulfenamides

The following procedures have been used to synthesize aliphatic sulfenamides:

1) The reaction of sulfenyl halides or sulfur halides with ammonia or primary or secondary amines in the presence of caustic or excess amine (1,4,7,8,10,11,12,13,14,33):

$$RSX + HNR'_2 \xrightarrow{-HX} RSNR'_2$$

A solution of the sulfenyl halide is prepared just before use by halogenating an appropriate sulfur compound such as a mercaptan, mercaptide, or a disulfide at about room temperature. Disulfides are often preferred because no hydrogen halide is evolved (10). With mercaptans, the hydrogen halide evolved is a nuisance and must be removed without destroying the sulfenyl halide.

$$RSSR + X_2 \xrightarrow{\text{ca. } 25^\circ} 2\ RSX$$

$$RSH + X_2 \xrightarrow{\text{ca. } 25^\circ} RSX + HX$$

$$RSM \text{ or } (RS)_2M \xrightarrow{Cl_2,\ Br_2} 2\ RSX$$

Preferably:

R= t-Butyl or trichloromethyl

M= Pb, Hg

The solution of the sulfenyl halide is caused to react with ammonia or an amine in the presence of excess amine, aqueous caustic, or other added proton acceptors in order to remove HX. The sulfenamide is then separated from the solvent system by any appropriate means. Yields range from 50 to 98%, depending upon the nature of the sulfenyl halide and that of the amine. No mechanistic studies of the reaction have been reported. The method appears to be quite general, particularly for sulfenyl groups containing no α-hydrogen atoms. It should be noted that sulfenyl halides have been caused to react with polyamines, particularly diamines (8,13,33), to yield molecules with more than one sulfenamide linkage.

Himel and Edmonds report in a patent disclosure that, in the reaction of one mole of sulfenyl halide with one mole of amine in the presence of one mole of aqueous sodium hydroxide at 25-50°, the rate of reaction with the amine exceeds the rate of hydrolysis of the sulfenyl halide (12). However, no supporting kinetic data are reported.

2) The reaction of mercaptans or mercaptides with thiocyanoamines (prepared by thiocyanation of amines) as reported by Peyron and Laplaine (2):

$$R'SH + NCSNR_2 \rightarrow R'SNR_2 + HSCN$$

$$\text{or } R'SM \qquad\qquad \text{or } MSCN$$

Only one study reports the use of this method. The yields are comparable to those obtained through the sulfenyl halides. The method appears to be general except where disulfide formation becomes competitive. The t-butylsulfenyl group was coupled successfully with several thiocyanoamines, but the following sulfenyl groups yielded disulfides: carboxymethyl, p-anisyl, and benzyl.

Parenthetically, it should be noted that the thiocyanoamines, discovered by Söderbäck in 1919 (15), could be considered as sulfenamides. However, it is beyond the scope of the seminar to discuss them except where they are used in syntheses of sulfenamides (3).

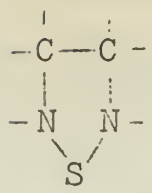
3) The action of chloramines or chloramides on mercaptans, mercaptides, or alkali sulfides (16,17):

$$RSH + ClNR'_2 \rightarrow RSNR'_2 + HCl$$

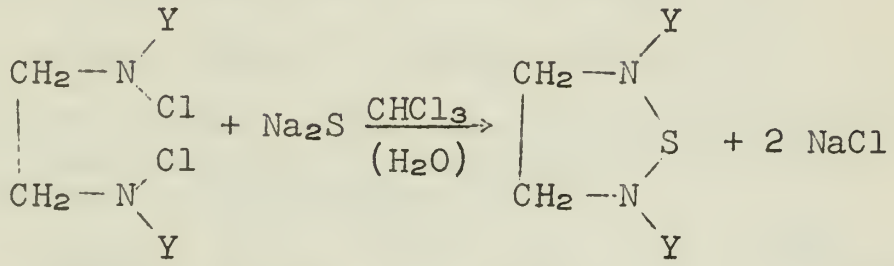
$$\text{or } RSM \qquad\qquad \text{or } MCl$$

$$R_2NCl + NaSNa + ClNR_2 \rightarrow R_2NSNR_2 + 2\ NaCl$$

Peyron (16) reports the synthesis of the heterocyclic 1,2,5-thiadiazolidines which may be considered to be cyclic "sulfendiamides". Peyron



caused sodium sulfide to react with appropriate 1,2-bis(chloramides) to close the heterocyclic ring:



Y= $CO\emptyset$, $SO_2\emptyset$, $COCH_3$

No yields are given and no proof of structure has been provided.

One older patent claims the synthesis of N-unsubstituted t-alkylsulfenamides from the t-alkyl mercaptan and monochloramine in "good yield". Details are lacking (17).

In addition to the aforementioned methods for synthesizing aliphatic sulfenamides, several other methods have been used to make aromatic and thiocarbamylsulfenamides.

1.) The reaction of a mercaptan, mercaptide, or disulfide with an amine in the presence of a suitable oxidizing agent (MOCl, H_2O_2, $K_2S_2O_8$, ferricyanide, X_2, etc.) (1,4,5,7,18):

(a) $ArSH + HNR_2 \xrightarrow{[O]} ArSNR_2 + H_2O$

(b) $ArSSAr + 2HNR_2 \xrightarrow{[O]} 2ArSNR_2 + H_2O$

An oxidizing agent need not be used with some aromatic disulfides, but then half of the sulfenyl groups are converted to sulfenamide and the remainder to mercaptide anion. For complete conversion to sulfenamides and better yields, an oxidizing agent is added. It should be noted that most researchers in the field have ignored the possible role of atmospheric oxygen and have made no provisions for eliminating this complication. Method (a) is felt to be of little applicability in the aliphatic series (4), the reaction being dependent on the case of proton loss and the basicity of the amine. Kharasch has shown that mixtures of benzyl mercaptan and alkylamines in the presence of an oxidizing agent invariably yielded benzyl disulfide in yields of over 90%. No mention is made as to whether more strenuous conditions caused the resulting disulfide to be converted to the sulfenamide. Some aromatic thiols may be caused to react with amines at least as basic as ammonia, under mildly alkaline conditions with hypochlorite, to yield sulfenamides. At slightly higher temperatures, thiuram disulfides may be caused to react with alkylamines in the presence of hypochlorite to yield alkylthiocarbamylsulfenamides (9).

2) Amine interchange between a sulfenamide not substituted on nitrogen and an amine whereby ammonia is replaced (1,4):

$$ArSNH_2 + HNR_2 \rightarrow ArSNR_2 + NH_3$$

The interchange can also be used, under suitable conditions, to replace one amino group with another (1).

3) The reaction of an arylthiocyanate with an amine (1):

$$ArSCN + 2HNR_2 \rightarrow Ar\ SNR_2 + HNR_2 . HCN$$

4) The condensation of carbonyl compounds with N-unsubstituted arylsulfenamides to form analogs of oximino ethers or Schiff's bases, sulfenimides, and thence to sulfenamides (1,4):

$$ArSNH_2 + OHCAr' \xrightarrow[-H_2O]{\triangle} ArSN = CHAr' \xrightarrow{[H]} ArSNHCH_2Ar'$$

In view of the fact that some reported reactions of thiocarbamyl-sulfenamides with aliphatic carbonyl compounds yield complex products (9,27), the reaction may not be applicable in the aliphatic series.

5) The reaction between a sulfenic ester and an amine (4):

$$ArSOR + HNR_2 \rightarrow ArSNR_2 + HOR$$

B. Reactions of Sulfenamides

Not many of the reactions of aliphatic sulfenamides have been investigated in detail. Some of the reactions mentioned in this section have been applied only to aromatic sulfenamides. Where possible, analogies will be drawn.

When oxidized carefully with, for example, hydrogen peroxide or potassium permanganate, sulfenamides may be converted to the well known sulfonamides. This reaction, used mainly in the aromatic series, has not been employed very often for proof of structure (1,4), probably because the reaction is said to be complex and hydrolysis may be competitive (4). Oxidation of arylsulfenamides with nitric acid has been reported to occur readily (4,19).

Mild reduction of aromatic sulfenamides is said to liberate ammonia and regenerate the disulfide (1):

$$2ArSNH_2 \xrightarrow{[H]} ArSSAr + 2NH_3$$

Stronger reducing agents acting upon a substituted arylsulfenamide result in the formation of the amine and mercaptan (18).

The reaction of aromatic sulfenamides with alcoholic alkali is reported to proceed as follows (1):

$$3ArSNH_2 + EtOH + 4KOH \rightarrow ArOEt + H_2O + 2ArSK + K_2SO_4 + 2NH_3$$

Aliphatic sulfenamides are hydrolyzed by aqueous mineral acids (4). Rheinboldt showed that aliphatic sulfenamides are cleaved nearly

quantitatively by anhydrous halogen acids (HBr and HCl) to the corresponding amine hydrohalide and sulfenyl halide (8). Such a reaction could be considered to be the reversal of the formation of a sulfenamide from a sulfenyl halide and an amine. The amine salt could be removed and the residual sulfenyl halide, in solution, could be coupled to another amine. Alternatively, the sulfenyl halide could be distilled, but decomposed readily. Following cleavage in the aromatic series, some unstable sulfenyl halides have been shown to go to the disulfides (4).

Arylsulfenamides unsubstituted on nitrogen are reported to condense with carbonyl compounds to form analogs of oximino ethers or Schiff's bases (1,4,18):

$$ArSNH_2 + OHCAr' \xrightarrow[-H_2O]{\triangle} ArSN = CHAr'$$

$$ArSN = CHAr' \xrightarrow[H_2]{HCl} ArSSAr + Ar'CH = NH \cdot HCl$$

Reductive hydrohalogenation may then proceed as outlined above.

2-Benzothiazolesulfenamides monosubstituted on nitrogen are cleaved by carbon disulfide to yield benzothiazole-2-thiol and the corresponding isothiocyanate (18) with elimination of sulfur.

Nitroarylsulfenamides are reported to react with thiosulfate ion to form sulfenylthiosulfates (20):

$$ArSNR_2 + S_2O_3^{=} + 2H^+ \rightarrow ArSS_2O_3^- + R_2NH_2^+$$

The reaction has been made the basis of a quantitative iodometric analysis. The application of the analysis to the aliphatic series is not reported.

N-Methyl-t-butylsulfenamide has been successfully benzoylated with m-nitrobenzoyl chloride over a period of 12 hours at room temperature in pyridine (8).

The decomposition of sulfenamides has often been attributed to rearrangements (4,9). When heated, members of the aromatic series are known to rearrange to secondary amines containing a thiol group or to sulfides containing an amino group (4). Some reaction paths have been suggested but they are beyond the scope of this seminar. For further details on arylsulfenamide rearrangements, see reference (4). In the aliphatic series, only thiocarbamylsulfenamides have been studied with success regarding decomposition products (9). Loss of sulfur with production of thioureas is the most recognized occurrence.

$$R_2NCSNR_2' \xrightarrow[\text{aging}]{\triangle \text{ or}} R_2NCNR'_2 + S$$

For the most part, the route of decomposition of sulfenamides is obscure.

C. Tabulation of Aliphatic Sulfenamides.

Many of the aliphatic sulfenamides reported in the literature are listed in Table I. A few compounds of obscure origin and indefinite existence as claimed in patents are excluded from the list.

The brevity of the table is noteworthy. Only about a dozen compounds may be said to be adequately characterized. Some sulfenamides, notably N, N-pentamethylene-t-butylsulfenamide (from t-butyl mercaptan and piperidine), were synthesized by more than one method. Beyond this, no structure proofs are given.

D. Patent Literature on Aliphatic Sulfenamides.

There is extensive patent literature covering aliphatic sulfenamides (1,4,7,12,13,14,21,22,23,24). It is, however, generally undetailed and will not be reviewed here. In addition to claiming the specific sulfenamides listed in Table I or processes for making the same, these patents claim alkylsulfenamides as accelerators for curing rubber, as lubricating oil additives, antioxidants, corrosion inhibitors, and organic intermediates.

II. ALIPHATIC THIOSULFENAMIDES

There are four references mentioning aliphatic thiosulfenamides (7,10,13,25), but the patent disclosures of Himel and Edmonds alone give any details (7,25). t-Butylthiosulfenyl chloride is made from t-butyl disulfide by chlorination in inert solvent at -40°. The resulting thiosulfenyl chloride is then caused to react with a suitable amine to yield a thiosulfenamide just as a sulfenyl chloride is used to synthesize a sulfenamide (10):

$$\text{t-BuSS-t-Bu} \xrightarrow[\substack{-40^\circ \\ \text{isopentane}}]{Cl_2} \text{t-BuSSCl} \xrightarrow[-HCl]{HNR_2} \text{t-BuSSNR}_2$$

The other product from the chlorination of the disulfide at low temperatures is reported to be t-butyl chloride (7). However, no attempts to isolate it are reported.

Chlorination of t-butyl disulfide at different temperatures has been investigated (7). The relative yields of sulfenyl and thiosulfenyl chlorides were determined by isolation of the corresponding piperidine derivatives.

		CHLORIDE, %	
RUN	TEMPERATURE	THIOSULFENYL	SULFENYL
1	-75°	89	8
2	-45	77	19
3	0	31	65
4	30	13	83

By a slightly different procedure for isolating the sulfenyl chloride formed, it was shown that yields of t-butylsulfenyl chloride drop to below 30% at a chlorination temperature of 150°.

Table II is a list of the thiosulfenamides claimed in the patents. The 80% yield claimed for N, N-diethyl-t-butylthiosulfenamide is noteworthy. Some data on the elemental analyses of the thiosulfenamides claimed are included in the patents and physical constants for the thiosulfenamides are mentioned.

III. ALIPHATIC THIOCARBAMYLSULFENAMIDES

In 1949, Smith, Alliger, Carr, and Young reported the synthesis of a series of thiocarbamylsulfenamides (9), the work growing out of interest in sulfenamide derivatives of thiazole and benzothiazole (18). Thiocarbamylsulfenamides are produced by the coupling of a dithiocarbamate with an amine or a chloramine:

$$R_2NH \xrightarrow[NaOH]{CS_2} R_2NC(=S)SNa \xrightarrow[\text{or } ClNR'_2]{HNR'_2,\ I_3^-} R_2NC(=S)SNR'_2$$

It should be noted that the intermediate dithiocarbamates are most easily made in the aliphatic series.

The thiocarbamylsulfenamides have properties similar to aliphatic sulfenamides. The lower members of the series are liquid and the higher members tend to be crystalline. Like sulfenamides, thiocarbamylsulfenamides generally are colorless when first prepared but tend to color with aging. They are sensitive to heat and acids. Evidence of decomposition has been observed within a matter of weeks or even, in some cases, within a few hours at room temperature (9). In contradistinction to sulfenamides, some of the decomposition products of thiocarbamylsulfenamides are known.

The following procedures have been used to synthesize thiocarbamylsulfenamides:

1) Oxidative coupling of an amine and a dithiocarbamate made from the same or a different amine (9,28):

$$R_2NC(=S)SNa + HNR'_2 \xrightarrow[I_2\ ,\ KI]{25\text{-}50^\circ} R_2NC(=S)SNR'_2 + NaOH$$

This method appears to be quite general. A solution of the dithiocarbamate is prepared from the amine, carbon disulfide, and sodium hydroxide. This solution and an excess of a second amine can then be coupled by means of an excess of the oxidizing agent. It is claimed that oxidizing agents other than iodine can be used to oxidize mixtures of dithiocarbamates or mercaptides and amines, but then disulfide formation may be competitive (9). The appearance of extensive amounts of disulfide in the final product is not a serious disadvantage of the iodine method. Yields range from 30 to 90%.

The added oxidizing agent may serve to convert the dithiocarbamate to a thiuram disulfide which may be a by-product or an intermediate. For example, it was shown that by-product disulfide in the reaction mass could be converted to sulfenamide by using a slightly higher temperature (9). The further course of the reaction is obscure at present.

2) The reaction of a dithiocarbamate with a chloramine (9,26):

$$R_2NCSNa + ClNR'_2 \rightarrow R_2NCSNR'_2 + NaCl$$

The method appears to be general but suffers in that a chloramine derivative normally must be prepared as an intermediate. The yield of sulfenamide was shown to parallel the yield of chloramine where the latter was not first isolated (9). No disulfide formation was noted.

3) The reaction of ammonia or an amine with a dithiocarbamate in the presence of hypochlorite (9):

$$R_2NCSNa + NH_3 \xrightarrow[\text{NaOCl (excess)}]{[O]} R_2NCSNH_2 + NaOH$$

The reaction may proceed through a chloramine. Normally, disulfide formation is appreciable by this route, unlike that observed in the thiazole series (18).

$$2\ R_2NCSNa \xrightarrow[\text{or } Cl_2]{NaOCl} R_2NCSSCNR_2$$

The thiuram disulfide is not converted to the thiocarbamylsulfenamide unless the reaction is completed at a slightly higher temperature. A similar reaction was noted when chlorine was used as oxidizing agent. However, in one case a dithiocarbamate was successfully coupled with an amine in the presence of hypochlorite when the hypochlorite (always in excess) and dithiocarbamate were added to the amine. In this case, the reaction probably proceeded through the chloramine.

The optimum conditions for syntheses of thiocarbamylsulfenamides are tabulated below (9):

	ROUTE 1 Oxidative Condensation	ROUTE 2 Chloramine
Temperature, ° C	0-50	-10 to +10
pH	12-12.5	13
[RSM], M	ca. 0.5	2-3
[Amine]/[RSM]	1.25-5	1.10-1.25

B. Reactions of Thiocarbamylsulfenamides.

The reactions of alkylthiocarbamylsulfenamides appear to be

analogous to those of alkylsulfenamides. The stability of thiocarbamylsulfenamides has already been mentioned. On long standing or heating, thiocarbamylsulfenamides generally decompose to thioureas through loss of sulfur (9,30,31):

$$R_2NCSNR'_2 \xrightarrow[\text{aging}]{\triangle \text{ or}} R_2NCNR'_2 + S$$

The only identified products were the thiourea and sulfur. In comparison, thiazole-derived sulfenamides decompose to disulfides. The reaction products of thiocarbamylsulfenamides with acids have not been identified. Of interest is the following observed reaction, notable for the formation of a symmetrically substituted thiourea from an unsymmetrical thiocarbamylsulfenamide (9):

$$(CH_3)_2NCSNHC_6H_{11} \xrightarrow{80\text{-}100^\circ} C_6H_{11}NHCNHC_6H_{11}$$

Other products of the reaction were not identified.

Cyclic thiocarbamylsulfenamides are known, having been prepared by the following scheme (28,31):

N,N'-Dialkylethylenediamines (I) $\xrightarrow{CS_2}$ R-N(CH$_2$-CH$_2$)NH$_2$-R, C(=S)S$^{\ominus}$ (II): N-Alkyl-N'-(β-alkylaminoethyl)dithiocarbamic acid, inner salts

II $\xrightarrow[I_3^-]{[O]}$ 2,5-Dialkyltetrahydro-1,2,5-thiadiazine-6-thiones (III)

III $\rightarrow$ 1,3-dialkyl-2-imidazolidinethiones (IV)

The cyclic thiocarbamylsulfenamides III could be decomposed by heat or aging with loss of sulfur to 1,3-dialkyl-2-imidazolidinethiones IV, cyclic thioureas. Models indicate the 6-membered thiadiazine ring to be strain-free.

Extensive patent literature exists regarding alkylthiocarbamylsulfenamides (9,26,27,29). Such literature is generally undetailed and is not reviewed further here (see reference 9 for more complete listings). The sulfenamides are generally claimed as vulcanization accelerators.

Two interesting species of arylsulfenamides analogous to thiocarbamylsulfenamides have been postulated as intermediates (30):

$$ArCYSNa + H_2NR \xrightarrow{[O]} [ArCYSNHR] \xrightarrow{-S} ArCYNHR$$

Y = O,S

The evidence is not conclusive. Even in the aromatic series the sulfenamides are expected to be unstable, decomposing to amides or thioamides.

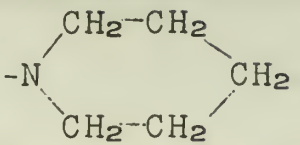
It should be noted that no references were found pertaining to infrared studies of aliphatic sulfenamides.

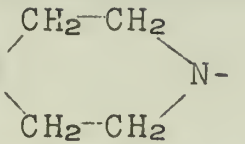
TABLE I

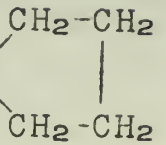
ALIPHATIC SULFENAMIDES

No.	Sulfenamide	Formula	Prep.	Yield	Properties	Remarks	Ref.
1	N-Methyl-t-butyl	t-BuSNHMe	RSI	54-8%	Bp 65/80 mm (ca. 124 at 760 mm with d.)	Amine odor, colorless	(8)
2	N,N-Dimethyl-t-butyl	t-BuSNMe$_2$	RSI	47-51	Bp 58.5/90 mm		(8)
			SCN	65	Bp 55/80 mm		(2)
3	N,N-Pentamethylene-t-butyl	t-BuSPipd	RSI		Bp 79/14 mm		(8)
			SCN	69	Bp 70/5 mm		(2)
			RSCl	98	Bp 55-6/4.5 mm	n_D^{20} 1.4765	(12)
4	1,4-Di(t-butylsulfenyl) piperazide	t-BuSPipzS-t-Bu	RSI		Mp 120		(8)
5	N,N-Pentamethylene-t-amyl	t-AmSPipd	RSI		Bp 100/12 mm	Colorless	(8)
6	N-Isopropyl-t-butyl	t-BuSNHCHMe$_2$	SCN	72	Bp 82/65 mm		(2)
7	N,N-Diethyl-n-butyl	n-BuSNEt$_2$	SCN	55	Bp 120/80 mm		(2)
8	1-(Carboxymethylsulfenyl)piperidide	HOOCCH$_2$SPipd	SCN	15	Bp 60/30 mm		(2)
9	N,N-Pentamethyleneethyl	EtSPipd	RSCl	74	Bp 50/7 mm	n_D^{20} 1.4900	(7)
10	N,N-Pentamethyleneisopropyl	Me$_2$CHSPipd	RSCl	82	Bp 60-1/8 mm	n_D^{20} 1.4812	(7)
11	N,N-Pentamethylene-t-hexyl	t-HexSPipd	RSCl	65	Bp 72-80/2 mm	n_D^{20} 1.4822-1.4862	(7)
12	N,N-Dimethyl-t-amyl	t-AmSNMe$_2$	RSCl	71	Bp 56.5/4 mm	n_D^{20} 1.4510	(7)
13	N,N-Bis(2-chloroethyl)trichloromethyl	CCl$_3$SN(CH$_2$CH$_2$Cl)$_2$	RSCl		Colorless oil, weak odor	Soluble HCCl$_3$, ØH	(11)
14	N,N-Tetramethylene-trichloromethyl	CCl$_3$SPyr	RSCl	39	Bp 68-70/1 mm		(33)
15	N,N-Pentamethylene-trichloromethyl	CCl$_3$SPipd	RSCl	55	Mp 29-30		(33)
16	N,N'-Bis(trichloromethylsulfenyl)-ethylenediamide	CCl$_3$SNHCH$_2$CH$_2$-NHSCCl$_3$	RSCl	53	Mp 42-43		(33)
17	1,4-Di(trichloromethylsulfenyl)-piperazide	CCl$_3$SPipzSCCl$_3$	RSCl	89	Mp 164-165		(33)
18	N,N-Di-n-dodecyl-t-butyl	t-BuSN(C$_{12}$H$_{25}$)$_2$	RSCl		Mp 34		(22)
19	N,N-Diallyl-t-butyl	t-BuSN(CH$_2$CH:CH$_2$)$_2$	RSCl		Bp 50-5/1.5-2 mm	n_D^{20} ca. 1.4762	(14)

NOTES:

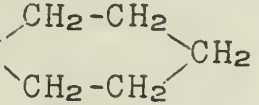
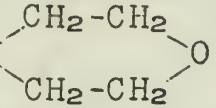
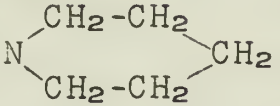
Pipd = 

Pipz = 

Pyr = 

RSX indicates via sulfenyl halide and amine.
SCN indicates via thiocyanoamine and mercaptide.
Boiling points at reduced pressure indicated with slash bar.

TABLE II
ALIPHATIC THIOSULFENAMIDES

No.	Thiosulfenamide	Formula	Prep.	Yield	Properties	Remarks	Ref.
1	N,N-Diethyl-t-butyl	t-BuSSNEt$_2$	RSSCl	80 %	Bp 60-3/0.5 mm	n_D^{20} 1.4995	(25)
2	N,N-Pentamethylene-t-butyl	t-BuSSN 	RSSCl		Bp 90/0.5 mm Bp 78/1 mm	n_D^{20} 1.5300 n_D^{20} 1.5210	(25) (7)
3	N,N-(3-Oxapentamethylene)-t-butyl	t-BuSSN 	RSSCl		Bp 90/0.5 mm	n_D^{20} 1.5280	(25)
4	N,N-Dimethyl-t-amyl	t-AmSSNMe$_2$	RSSCl		Bp 60-85/4 mm	n_D^{20} 1.5069	(7)
5	N,N-Pentamethylene-t-hexyl	t-HexSSN 	RSSCl				(7)

NOTES:

RSSCl denotes preparation via thiosulfenyl chloride and amine.
Boiling points at reduced pressure indicated by slash bar.

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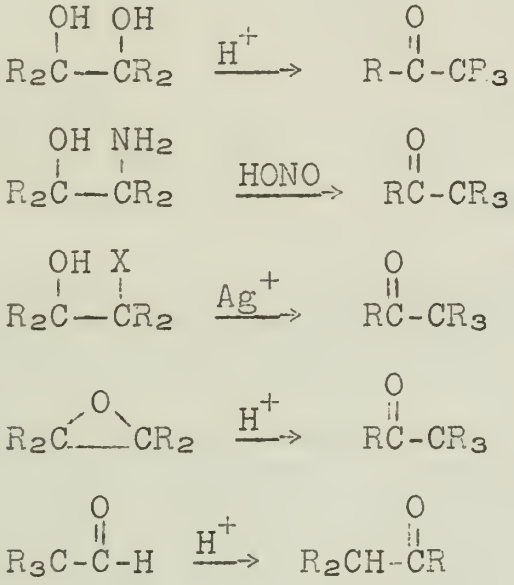
MECHANISM OF THE PINACOL-PINACOLONE REARRANGEMENT

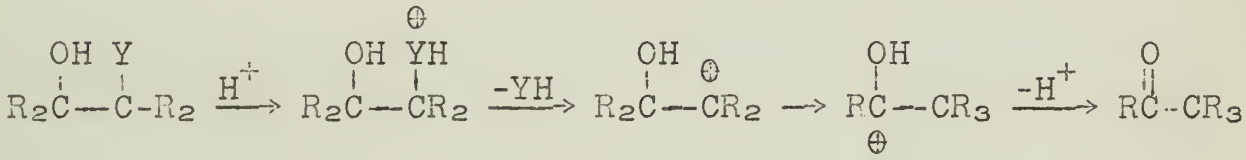
Reported by J. W. Hausser December 19, 1957

INTRODUCTION

There are a number of molecular rearrangements that proceed by mechanisms similar to that of the 1,2-shift in the pinacol rearrangement.



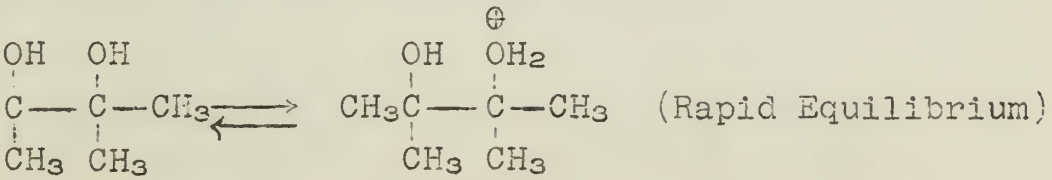
In 1932 Whitmore (1) postulated a series of steps as the mechanism of this class of rearrangements.

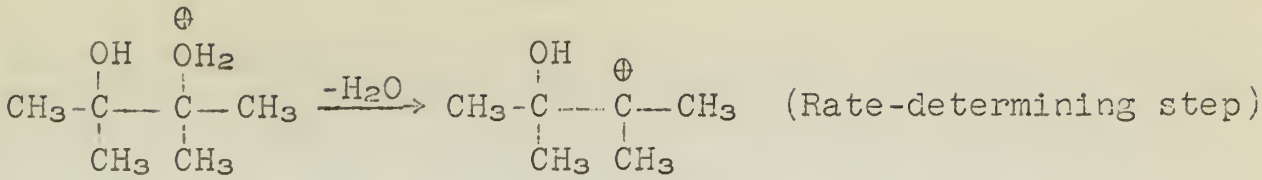


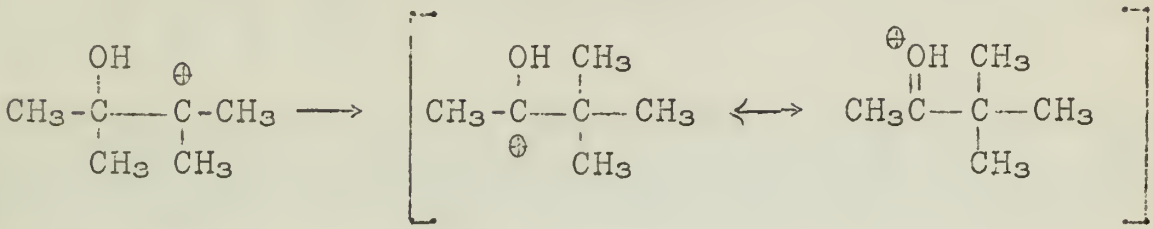
This seminar will be concerned with the pinacol rearrangement; other examples of 1,2-shifts will only be used to clarify general points.

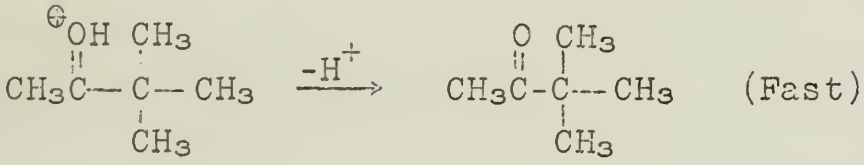
Mechanism of the Rearrangement of Pinacol.--The complexity of the pinacol rearrangement is such that a detailed study of the mechanism has only been made on simple glycols. Most of the work has been done on pinacol itself.

A mechanism for the rearrangement of pinacol that seems to be consistent with the observed data would be the following:



II 

III 

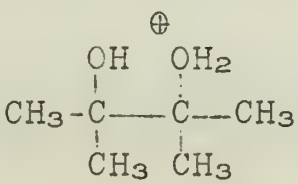
IV 

That step I is a rapid equilibrium is demonstrated by the rapid exchange of hydroxilic hydrogen atoms of pinacol in the presence of tritium oxide at room temperature (2).

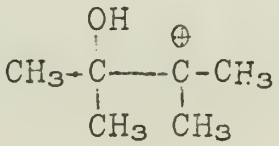
When the rearrangement was carried out in deuterium oxide and dilute acid, an increase in rate by a factor of about two was observed (2,3). If the simple isotope effect were operative, a decrease in rate should have been produced if oxygen-deuterium bonds were being broken or formed in the rate-determining step. In the above mechanism both steps I and IV involve either making or breaking of oxygen-hydrogen bonds, so we can conclude that they are not rate-determining steps.

The reaction is first order in pinacol in a medium of constant acidity (4-12). The reaction is specifically acid-catalyzed by hydronium ion, and bisulfate ion in particular has no catalysing effect (4), again verifying that step I is a rapid equilibrium. Application of the H_o acidity function to the reaction has proved to be quite helpful in arriving at certain mechanistic conclusions. The kinetics of the rearrangement have been determined for a number of different acids in the temperature range of 70° to 150°. A plot of $-H_o$ vs. log k_1 gives a straight line of slope near unity (4-12). No correlation is observed between C_o and log k_1 (6,7) (C_o is the acidity function based on the alcohol-carbonium ion equilibrium).

Since the rate constant is related to H_o, the transition state should look like the conjugate acid of pinacol (I), whereas if the rate constant could have been related to C_o, the transition state would look more like the carbonium ion (II) (6,7).



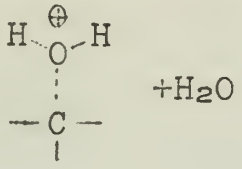
I



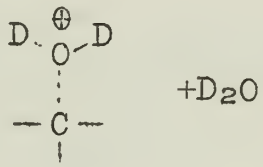
II

The rearrangement of 1,2-glycols can be considered to proceed by a spectrum of mechanisms. In one limiting case the transition state could look like I with most of the positive charge on oxygen and in the other limiting case like II with most of the positive charge on carbon. The transition state of pinacol approaches that of I.

This picture of the transition state (I) allows an explanation of the observed rate increase in deuterium oxide (2,3). The general observation that deutero-acids are weaker than proton-acids (3b) suggests that the undeuterated transition state (I)



I



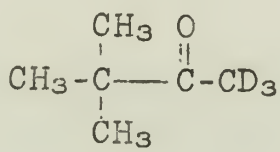
III

should be of lower stability than III. Since the transition state (III) is of lower free energy, the rate of reaction by loss of water should be increased and thereby the rate of rearrangement increased.

When pinacol is placed in $H_2{}^{18}O$ it is found to exchange ^{18}O very rapidly (13). At first appearance this would indicate that step II is an equilibrium. However, it is not established that the exchange of oxygen and the loss of water in rearrangement proceed by the same mechanism.

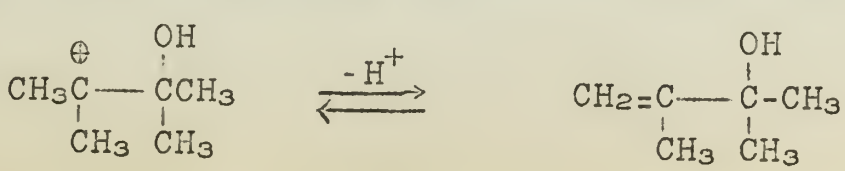
Step III consists of a rapid methyl migration. The driving force of the rearrangement is seen in this step since the product of migration is the resonance-stabilized conjugate acid of a carbonyl group.

An important consideration is the timing of steps II and III. Kinetic data will not determine whether or not the reaction is concerted. A product study of the rearrangement of pinacol in deuterium sulfate has failed to provide evidence for carbonium ion II (14). The rearrangement produced pinacolone (IV) which was deuterated only in the methyl fragment.



IV

If the open carbonium ion (V) were formed, it is possible that it would have eliminated a proton forming olefin, and subsequently added a deuteron giving rise to deuterium exchange.



V

This exchange would lead to deuteration in the t-butyl group. This was not observed. However, this evidence does not exclude a non-concerted mechanism since exchange would not occur if the rate of methyl migration (step III) is rapid with respect to proton elimination. Deuterium in the methyl group is explained by the enclization of pinacolone.

One conclusion that can be drawn from this work is that step III is irreversible under the reaction conditions employed, for if it were reversible, the deuterated methyl could have migrated back to give deuterium in the t-butyl group.

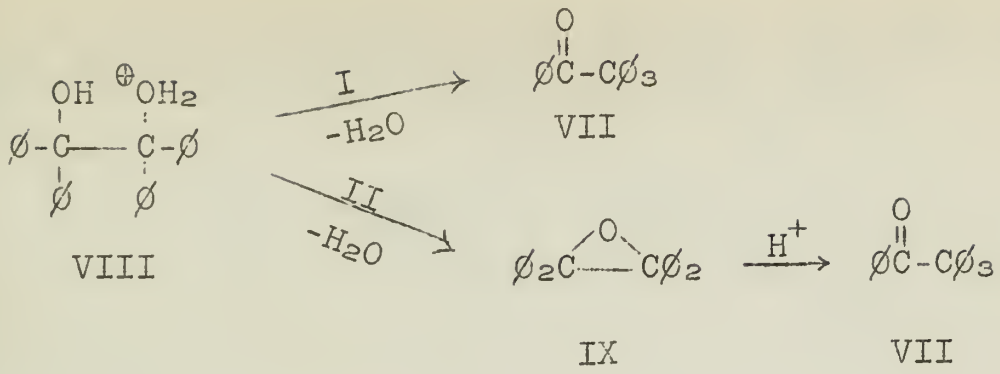
The best evidence for a non-concerted reaction is found in the structurally similar 1,2-dimethyl-1,2-cyclohexanediol system (17). The cis- and trans-isomers rearrange non-stereospecifically to form 1-acetyl-1-methylcyclopentane, indicating the presence of a common intermediate. A non-concerted mechanism is thus in accord with all experimental evidence.

An attempt to elucidate the nature of steps II and III was undertaken by Duncan and Lynn (13,15) by the use of ^{14}C isotopes. Pinacols were prepared with ^{14}C in the methyl groups and ^{14}C replacing the alcoholic carbon atoms. At 100° the methyl substituted pinacol was reported to give an isotope effect of 0.47, and the alcoholic substituted pinacol an isotope effect of 0.73. The magnitude of these effects seems to be quite large; however, emperical calculations were considered to indicate that an effect of this magnitude is possible. At temperatures of 50° to 60° the isotope effect was reported to be only about 2%. Further work seems to be desirable to verify these results before definite conclusions are in order.

Mechanism of the Rearrangement of Benzopinacol.--As the groups on the glycol in a pinacol rearrangement are changed, a variation in mechanism occurs. Another simple pinacol which has been studied is benzopinacol (VI) (16).

VI VII

A kinetic study of the rearrangement showed that the rate of appearance of product (VII) was slower than the rate of disappearance of the starting material (VI). This lag is indicative of an intermediate. The workers isolated tetraphenylethylene oxide from the reaction medium. The best explanation for the rearrangement involves the competition of two concurrent reactions. The conjugate acid of benzopinacol (VIII) can either go directly to product (VII) or form the intermediate oxide (IX) which then rearranges to p-benzopinacol (VII).



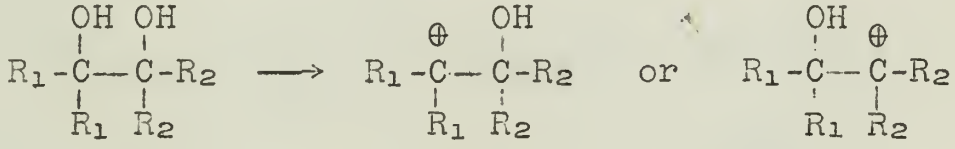
VIII VII IX VII

It was estimated that 80% of the reaction proceeded through the epoxide. In this system neighboring group participation plays an important role, with hydroxyl being sterically favored for participation.

MIGRATION RATIOS

The term "migration ratio" is used to express the relative tendency of substituents to undergo a shift within the molecule, but so many factors affect the ratio that it is not useful. (For a summary of migration ratios see Newman (18)).

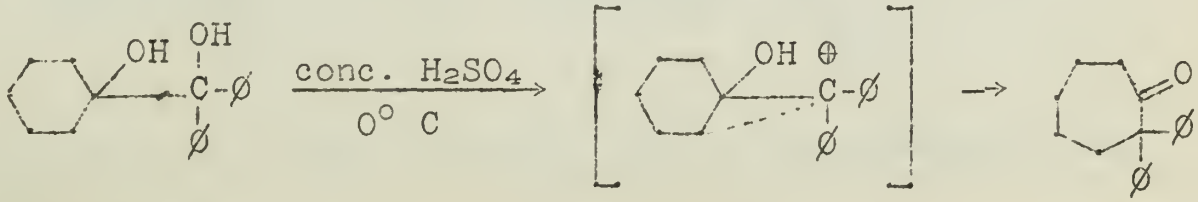
Formation of the Carbonium Ion Intermediate.--The rearrangement of the unsymmetrical pinacol (X) could form one of the two intermediate carbonium ions (XI) or (XII).



X XI XII

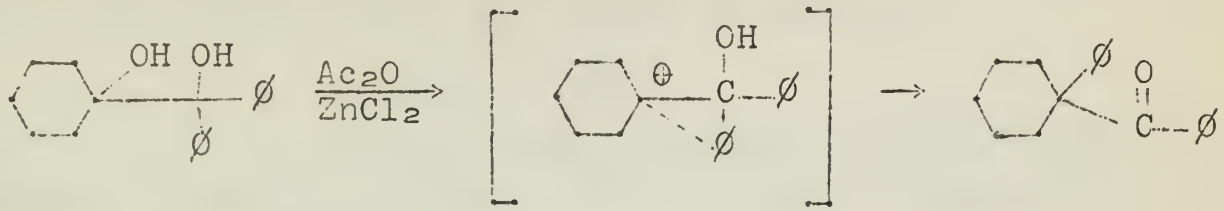
Experimental evidence supports the general rule (19) that hydroxyl loss is facilitated by both inductive and conjugative electron release of the α-substituents. The order of carbonium ion stabilization is aryl > alkyl > hydrogen. The unsymmetrical pinacols (X) have been studied (18), and in many cases the product is that formed by a simple rearrangement of the more stable initial carbonium ion; however, medium effects may be important.

Medium Effects.--1-Hydroxy-1-cyclohexyldiphenyl carbinol (XIII) (20,21,22) in concentrated sulfuric acid at 0° has been found to undergo rearrangement through a sequence that would require the formation of the more stable carbonium ion intermediate (XIV) followed by a methylene migration.



XIII XIV

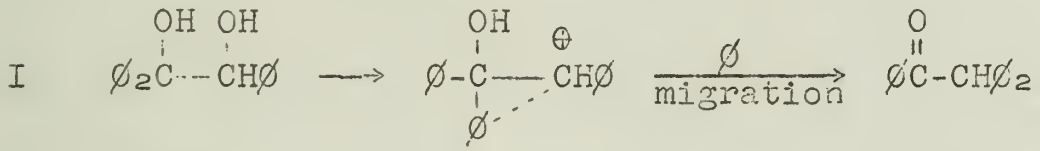
In acetic anhydride containing zinc chloride the rearrangement occurs with phenyl migration, indicating that the intermediate (XV) of lower stability could have been formed.



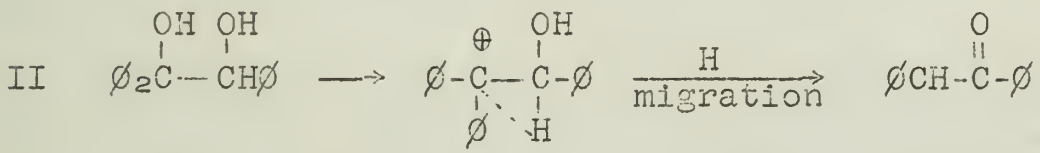
XIII XV

The actual mechanism is probably quite complex, since a simple explanation is not apparent.

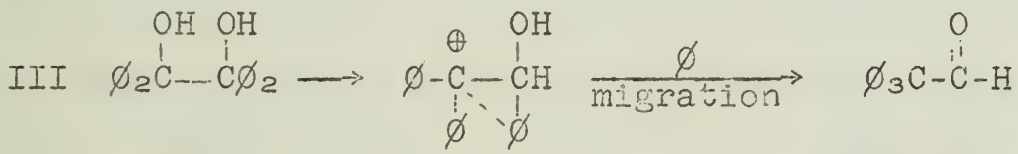
In the rearrangement of triphenylethylene glycol (XVI), two products were isolated, benzhydryl phenyl ketone (XVII) and triphenylacetaldehyde (XVIII) (23). Collins (24) has considered four possible reaction paths for the rearrangement.



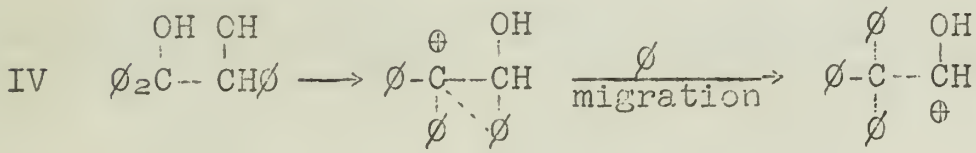
XVI XVII



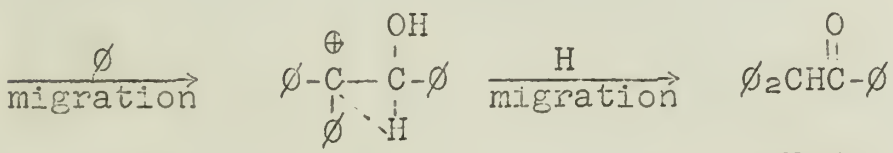
XVI XVII



XVI XVIII



XVI



XVII

The importance of each mechanism for the rearrangement was determined by the use of ^{14}C-labeling and was found to be dependent on the medium.

The reaction was carried out in various solvents ranging from concentrated sulfuric acid to dilute hydrochloric acid in aqueous dioxane. Table I summarizes the contribution from each path and gives the migration ratio of phenyl to hydrogen.

Table I (24)

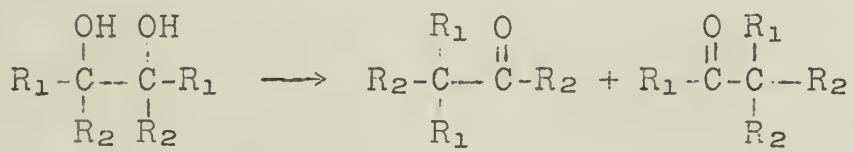
Medium	% Contribution of Path I	II	III	IV	Migration Ratio: Ø/H
Conc. H_2SO_4	2.5	11.7	0	85.8	7.33
Oxalic acid	2.7	29.9	29.9	37.5	2.25
Formic acid	4.7	39.0	0	56.3	1.44
Dil. H_2SO_4	3.2	67.4	16.5	12.9	0.435
HCl-Aq. Dioxane	0	96.1	3.9	0	0.0406

In order to determine the nature of hydrogen migration similar systems were considered. In o-tolylhydrobenzoin (25) and 1-phenyl-1-o-tolylethylene glycol (26) hydrogen was observed to migrate intramolecularly and in a concerted manner. The rearrangement of 1,2-dimethoxyisobutane in deuterated methanol gave isobutyraldehyde (4) in which 33% of the migrating hydrogen was replaced by deuterium. The hydrogen migration in this case was at least largely internal and possibly entirely internal since deuterium exchange could occur through enolization of isobutyraldehyde with small amounts of water. It follows then that hydrogen migration proceeds by an internal mechanism.

From Table I it is seen that as the ionizing strength of the medium decreases, hydrogen migration competes more favorably with phenyl migration. Thus it may be concluded that phenyl migrates in preference to hydrogen in this system when the reaction proceeds through an open carbonium ion, and hydrogen migrates in preference to phenyl when a concerted mechanism is operative.

This conclusion is consistent with what would be predicted from a consideration of steric factors. The rotational conformation of lowest energy would have the hydrogen and hydroxyl trans.

Competing Groups in Migration.--The relative ability of competing groups to migrate has been determined by a study of the rearrangement of symmetrical pinacols of type (XIX) (18).



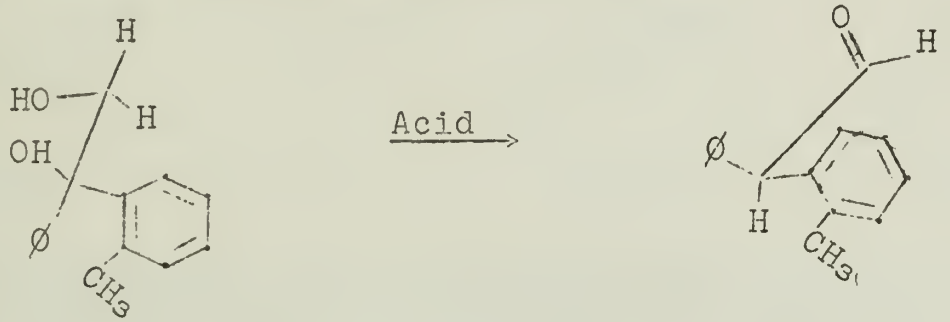
XIX XX XXI

A product analysis will show whether R_1 or R_2 migrated giving the products (XX) and (XXI) respectively. In this system intrinsic migration abilities may be calculated without question of the intermediate ion. The stereochemical complications will be considered later.

In aryl pinacols it is experimentally observed that migration is helped by substituents with $-\sigma$ values (26). A correlation of

migration ratios to Hammett's σ values has been made by McEwen and Mehta (26a) by plotting the log of the migration ratio vs. σ . Deviations from linearity are observed in the cases of p-alkyl and p-methoxyl groups. Somewhat better correlation was obtained by Okamoto and Brown (26b) when σ + values were used.

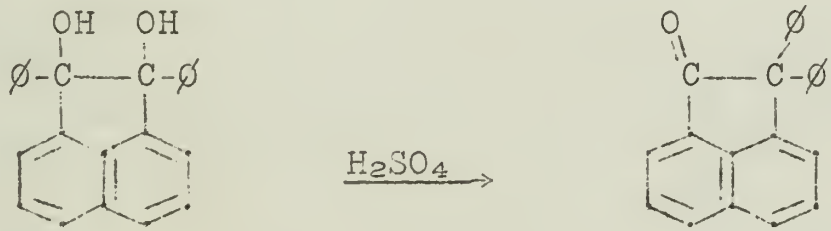
Steric Factors in the Pinacol Rearrangement.--The migration of hydrogen has been observed to proceed stereospecifically (26). For example (+)1-phenyl-1-o-tolylethylene glycol (XXII) rearranged to (+) phenyl-o-tolylacetaldehyde (XXIII).



XXII XXIII

Inversion took place at the asymmetric carbon atom.

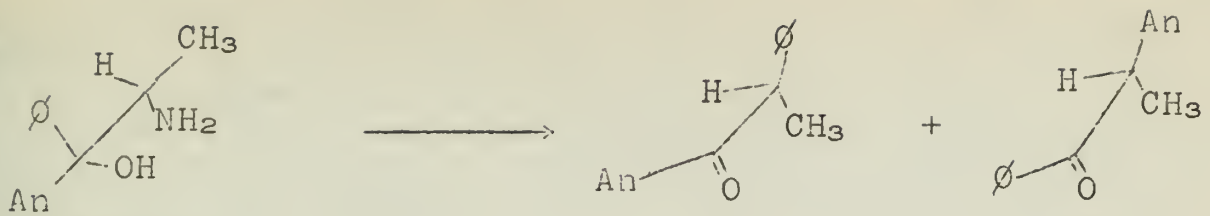
Bartlett and Brown (28-31) have worked on the rearrangement of cis- and trans-7,8-diphenylacenaphthene-7,8-diol (XXIV). Both isomers rearranged to give the same product (XXV).



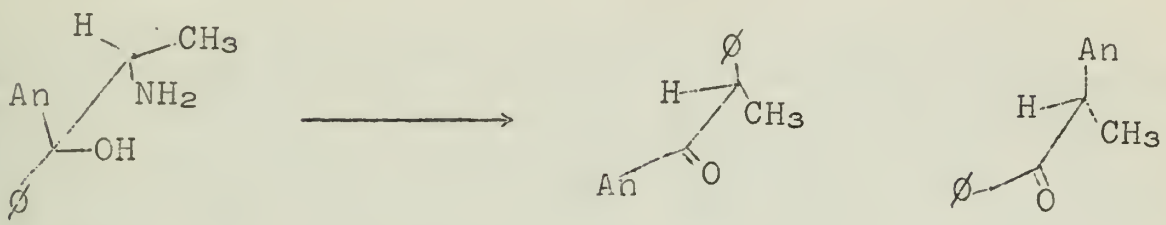
XXIV XXV

The rate of rearrangement of the cis-diol is six times as fast as the rate of rearrangement of the trans-diol. As the concentration of water increases the rates approach each other. Cis-diol was recovered from the reaction mixture of the pure trans-diol. These data have been interpreted as being evidence for phenyl participation. This means that the trans-isomer rearranges to the cis-isomer which then undergoes a pinacol rearrangement. It is not necessary to explain the rearrangement in this way. The observation may be readily explained by considering an intermediate carbonium ion which can give an equilibrium mixture of cis- and trans-diol, or rearrange to product. The cis-diol reacts more rapidly since there is a steric acceleration due to a relief in strain in going to the transition state.

In a study of the deamination of amino alcohols Curtin (32,33a) has attempted to separate electronic and steric effects. The erythro (XXVI) and threo (XXVII) forms of 1-anisyl-1-phenyl-2-aminopropanol were isolated and rearranged by nitrous acid deamination.



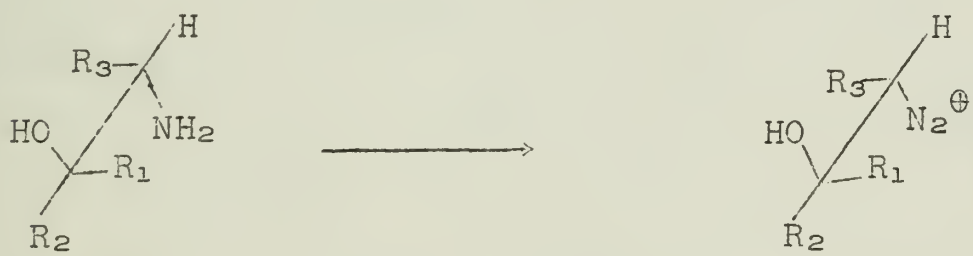
XXVI XXVIII XXIX



XXVII XXVIII XXIX

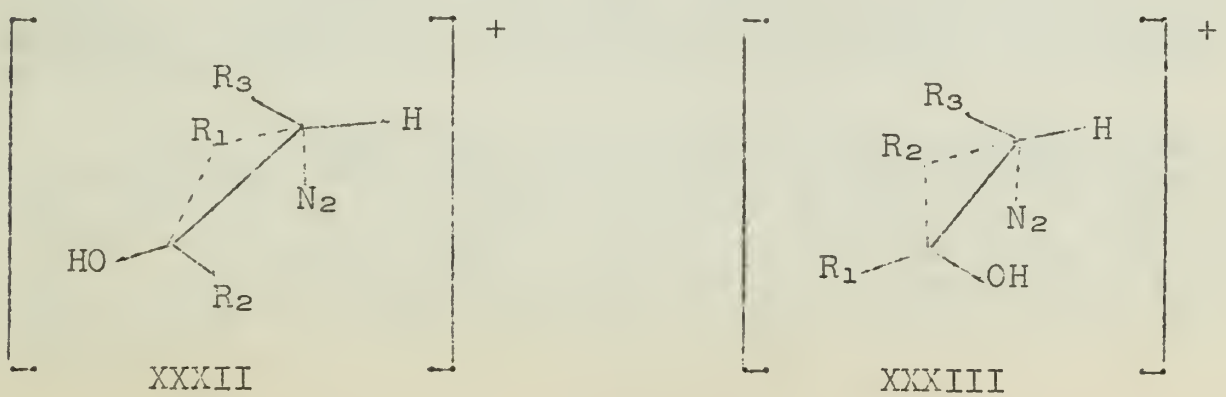
By considering the ratios of products (XXVIII and XXIX) in the two rearrangements, it was possible to separate a steric effect and an electronic effect since in the case of the erythro (XXVI), the electronic and steric factors are in opposition, whereas in the case of the threo (XXVII), the effects are in the same direction.

It was assumed that the first step in this rearrangement was the formation of the diazonium ion (XXXI) from the amine (XXX).



XXX XXXI

If it is assumed that the rotation about the central C-C bond is rapid with respect to rearrangement, then the stereospecificity of the rearrangement can be explained in terms of the "cis effect". The transition states possible when R_1 and R_2 migrate would be XXXII and XXXIII respectively.

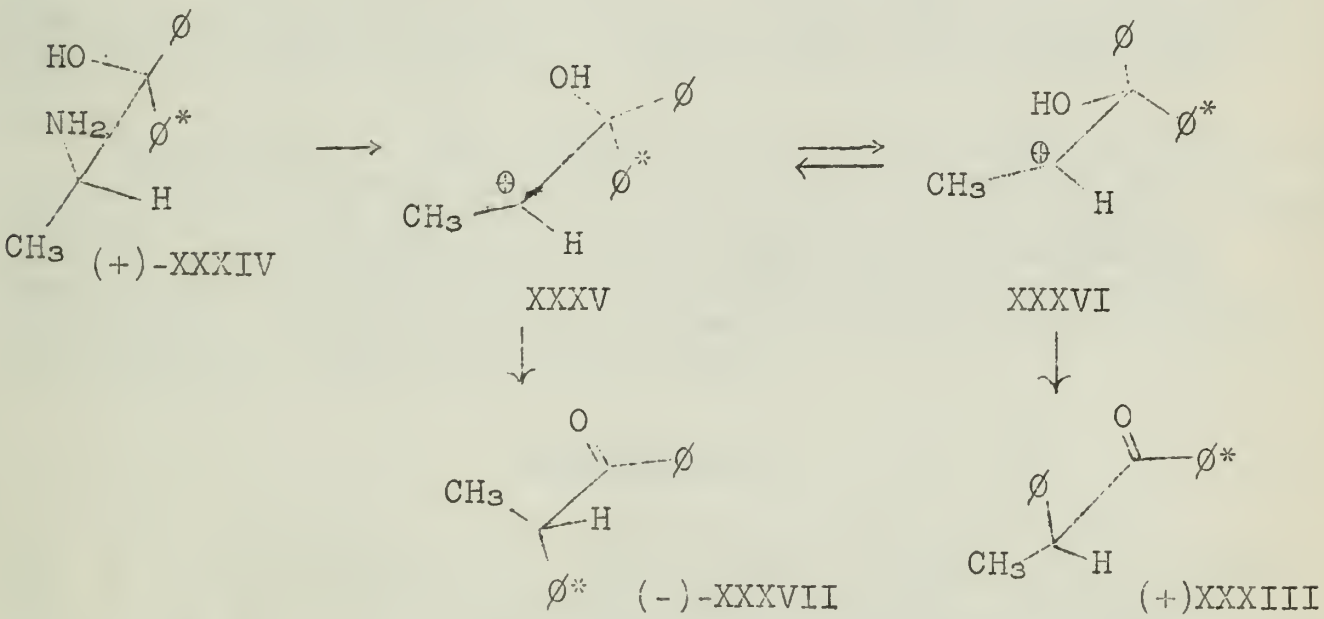


XXXII XXXIII

If rotation around the C-C bond is rapid, then the transition state will be independent of the configuration of the starting material. The free energy will be a function of the interaction of the non-migrating groups in the transition state. Thus the "cis effect", which includes factors such as steric inhibition of resonance, dipole-dipole interactions and entropy differences in going to the transition state, will determine the lowest energy transition state.

Streitweiser (34) has questioned the validity of the assumption that rotation is rapid with respect to rearrangement. The low activation energy for the loss of nitrogen suggests that rotation and migration proceed at comparable rates. If this is so, the configuration of the starting material will be important in determining the transition state. This does not affect the argument for the rearrangement of bromohydrins (33b).

Recent work by C. J. Collins (45) on nitrous acid deaminations of amino alcohols using isotopic labeling techniques has led to some interesting results. Pure rotational isomers of phenyl-labeled 1,1-diphenyl-2-aminopropanol (XXXIV) were separated and rearranged by nitrous acid deamination.



It was found that in the rearrangement of the (+)isomer of (XXIX), the labeled phenyl group migrates to give the inverted ketone ((-)-XXXII) in 88% yield. The unlabeled phenyl group migrates to give 12% of the product ((+)-XXXII) of retained configuration.

If one assumes that the migration occurs trans, then it can be concluded that the reaction proceeds through an open carbonium ion intermediate. The equilibration of structures XXV and XXXVI by rotation about the C-C bond is not faster than the rate of phenyl migration. This open carbonium ion has been demonstrated in other systems involving nitrous acid deamination (35,36,37).

Competing Reactions.--Reactions competing with the pinacol rearrangement may be considered in terms of neighboring group participation (38). One may observe anchimeric assistance by neighboring hydroxyl, neighboring carbon or hydrogen and, under the proper pH conditions, neighboring alcoholate ion, as well as solvolysis without neighboring group participation. The competition of neighboring group participation determines the nature of the products, so if one is able to control the participation by controlling the reaction conditions, optimum yields of the desired product may be attained.

One of the important competing reactions is the formation of epoxides. The order of participation is alcoholate ion > aryl > hydroxyl (39,40), so that epoxide formation would be favored by a weakly basic medium. For example, triphenylethylene oxide (39) is conveniently prepared from 1,1,2-triphenyl-2-bromoethanol by reaction with hydroxyl ion in either aqueous dioxane or ether, or with acetate ion in aqueous dioxane. Reaction of 1,1,2-triphenyl-2-bromoethanol with silver ion promotes phenyl participation, giving benzhydryl phenyl ketone.

The formation of a diene by dehydration is another competing reaction. Pinacol is formed in 65 to 72% yield by refluxing pinacol in 6N sulfuric acid (41). 2,3-Dimethyl-1,3-butadiene is prepared by heating pinacol or pinacolone with a small amount of concentrated hydrobromic acid (42). The yield is 55 to 60%.

Dehydration is also observed when the reaction is carried out in a mixture of acetyl chloride and acetic anhydride (43,44). The yield of diene is improved by lower pinacol concentration, higher ratio of acetyl chloride to acetic anhydride and increased temperature. In this case, a consistent mechanism for the dehydration is the formation of the monoacetate and subsequent elimination of water and acetic acid.

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ORGANOSILICON FREE RADICALS

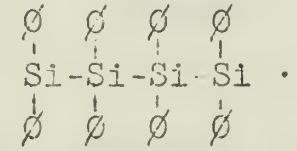
Reported by T. W. Milligan January 2, 1958

The possibility for the existence of free radicals of silicon, in analogy to those of carbon, was recognized early in the history of organosilicon chemistry.

This seminar will present a brief historical resume of the subject, and representative examples from the modern work illustrating the detection and reactions of some organosilicon radicals. The synthetic implications of the radical addition of silanes to unsaturated compounds, included in a very comprehensive recent review (1), and the photochemical halogenation of organosilanes will not be included.

EARLY EXAMPLES:

The first mention of silyl radicals was made by Kipping in 1923 (2). He obtained two isomeric silicohydrocarbons, $Si_4(C_6H_5)_8$, from the reaction of diphenyldichlorosilane with sodium. One of these (the "saturated" isomer) was assigned the structure of "octaphenylcyclosilicotetrane" on the basis of chemical evidence; the other (the "unsaturated" isomer) was postulated as a linear diradical.



This structure was assigned on the basis of the following evidence.

1. When boiled for 10 minutes with benzaldehyde or nitrobenzene the compound decomposed by oxidation. The same results were obtained if the compound was boiled in the presence of O_2 or acetophenone for longer periods. Two compounds of formulae $Si_4(C_6H_5)_8O_2$ and $Si_4(C_6H_5)_8O$ were isolated from these oxidations.

2. The compound reacted rapidly with iodine, tetrachloroethane, dibromoethylene and phosphorus tribromide to yield a dihalogen addition product.

3. The diiodo derivative thus formed could be ethylated with ethyl magnesium bromide, but phenyl magnesium bromide did not react. Kipping cited this as evidence that the terminal silicon atoms in the 4 membered chain were sterically shielded by the neighboring phenyl rings. The stability of the radical was also explained by this steric protection at the tervalent silicon atoms. Unfortunately no later work involving magnetic or spectroscopic measurements on this compound has been reported.

The product of the reaction of triphenylsilyl bromide with lithium in ethylamine was at first believed to be a solvated free radical $\emptyset_3Si\cdot EtNH_2$ (3), but later investigations showed it to be a silylamine $\emptyset_3SiNHEt$ (4).

THE ADDITION OF ORGANOSILYL RADICALS TO OLEFINS:

The radical addition of halomethanes to olefins is a well known reaction discovered by Kharasch. In 1947 two groups of investigators reported a similar reaction for trichlorosilane. Sommer, et al. (5), added Cl_3SiH to 1-octene using acetyl peroxide as an initiator, while Burkhard and Krieble (6) added Cl_3SiH to isobutylene and acetylene using t-butylperbenzoate. A Kharasch type chain mechanism was proposed for these reactions. Aryl and alkyl silanes have also been used (7,8,9,10,11).

$$Cl_3SiH + R'\cdot \longrightarrow R'H + Cl_3Si\cdot$$

$$RCH{=}CH_2 + Cl_3Si\cdot \longrightarrow RCH\text{-}CH_2SiCl_3$$

$$RCHCH_2SiCl_3 + Cl_3SiH \longrightarrow RCH_2CH_2SiCl_3 + \cdot SiCl_3$$

In the last 10 years reactions of this type have become important commercially in the production of carbon-silicon compounds; the reader is referred to a recent review (1) which covers the literature to January 1, 1955. A few examples of these reactions are listed in table I.

TABLE I ADDITION OF SILANES TO OLEFINS

Silane	Olefin	Product	Conditions	Yield	Ref.
Cl_3SiH	1-octene	$Cl_3Si(CH_2)_7CH_3$	Ac_2O_2, 11 hrs. at 50-63°	99%	5
$\emptyset_3SiH$	9-undecylenic acid	$\emptyset_3Si(CH_2)_{10}COOH$	Bz_2O_2, 14 hrs. at 70°	96%	7
CH_3SiCl_2H	ethylene	telomers	560 atm., 260-270°	80%	12
Cl_3SiH	ethyl vinyl ether	$Cl_3Si(CH_2)_2OEt$	hv, reflux 48 hrs.	53%	13

All of these reactions showed several common characteristics indicating their free radical nature. They required only catalytic amounts of peroxide. Alternatively, ultraviolet light (13), heat (12), or azo compounds (14) could be used to initiate the reactions. Reactive vinyl compounds such as styrene or acrylic esters gave poor yields, polymers being the major products. The recent work of Haszeldine (15,16,17) has been instructive in regard to the control of polymerization in the reaction with tetrafluoroethylene (see below).

As in the case of the Kharasch reaction, the rule for orientation seems to point toward terminal addition of the silyl radical whenever possible, probably because of the relative stabilities of the two possible intermediate radicals:

$$R\text{-}\underset{\cdot}{CH}\text{-}CH_2SiCl_3 \quad \text{more stable than} \quad R\text{-}\underset{\cdot}{CH}\text{-}CH_2\cdot \quad (SiCl_3)$$

Thus Speier has shown that the reaction of Cl_3SiH with 1-pentene (14) affords exclusively 1-trichlorosilyl pentane proved by conversion to the trimethylsilyl derivative identical with an authentic sample. A similar reaction with 2-pentene gave a mixture

of isomers in a 70/30 ratio (by gas chromatography) but their structures were not assigned. Gilman (18), Gadsby (7), and other workers have noticed a similar orientation effect using radicals from triphenylsilane and various alkyl, aryl and halo-substituted silanes.

It is interesting to note that trichlorosilane will react in poor yield with isobutylene (6), which contains no β-hydrogen atoms, while a similar reaction using chloroform does not occur.

The work of Haszeldine, Geyer, and co-workers (15,16,17a,17b), furnishes a useful illustration for this type of reaction. Trichlorosilane, dimethylsilane and methyldichlorosilane have been added to tetrafluoroethylene using ultraviolet light initiation. From dimethylsilane they obtained 3 types of products:

$$Me_2SiH_2 \xrightarrow{C_2F_4} Me_2Si\begin{matrix}H\\ CF_2CF_2H\end{matrix} \quad + \quad Me_2Si\begin{matrix}H\\ (CF_2CF_2)_nH\end{matrix} \quad + \quad Me_2Si\begin{matrix}(CF_2CF_2)_xH\\ (CF_2CF_2)_yH\end{matrix}$$

I II $n > 1$ $x \geq 1$, $y \geq 1$ III

The following mechanism was proposed:

$$Me_2SiH_2 \xrightarrow{h\nu} Me_2\dot{S}iH + H\cdot$$

$$Me_2\dot{S}iH + C_2F_4 \longrightarrow Me_2Si\begin{matrix}H\\ CF_2CF_2\cdot\end{matrix} \qquad \text{initiation}$$

$$Me_2\text{-}Si\begin{matrix}H\\ CF_2CF_2\cdot\end{matrix} + C_2F_4 \longrightarrow Me_2Si\begin{matrix}H\\ (CF_2CF_2)_n\cdot\end{matrix} \qquad \text{propagation}$$

$$Me_2Si\begin{matrix}H\\ (CF_2CF_2)_n\cdot\end{matrix} + MeSiH_2 \longrightarrow Me_2Si\begin{matrix}H\\ (CF_2CF_2)_nH\end{matrix} + Me_2\dot{S}iH$$

chain transfer

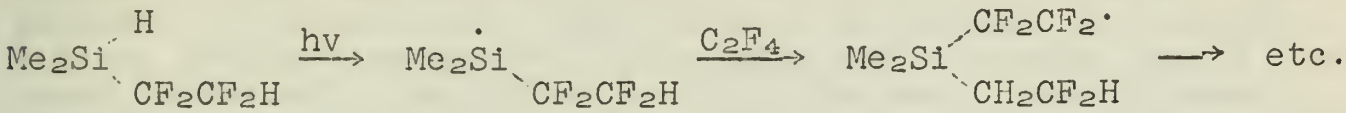
The absence of even traces of hydrogen from the products suggested to Haszeldine that the H atoms formed in the initial step must attack the olefin.

$$H\cdot + C_2F_4 \longrightarrow CHF_2CF_2\cdot \xrightarrow{MeSiH_2} CHF_2CF_2H + Me_2\dot{S}iH_2$$

In the absence of any evidence establishing the kinetic chain length, however, such a proposal as to the fate of the very reactive H atoms is not justified.

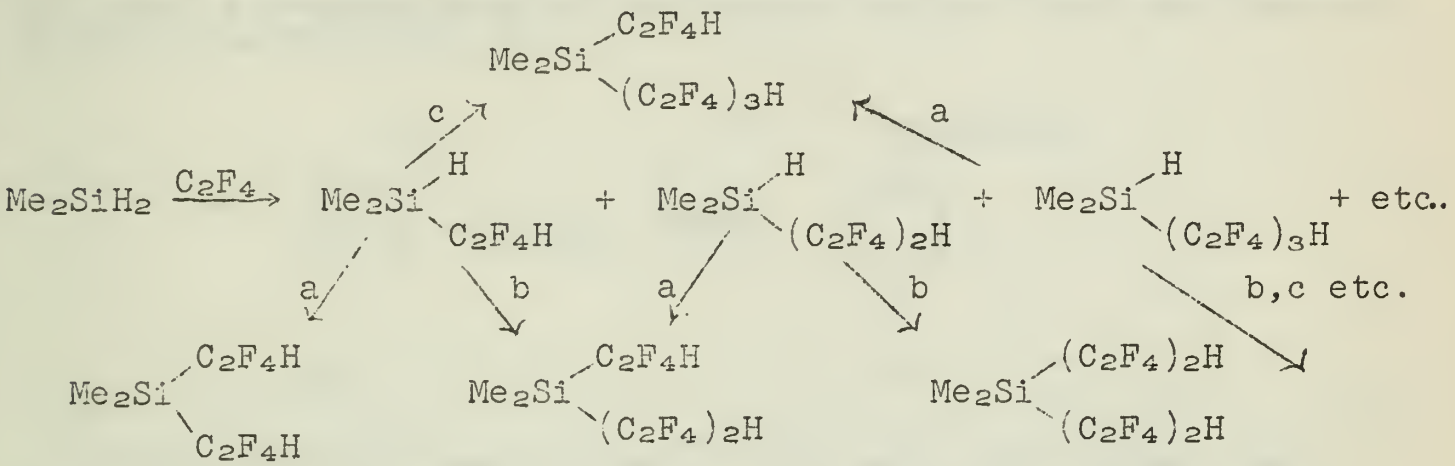
The main factor influencing the ratio of products was the mole ratio of starting materials, indicating the facility of the chain transfer step. For example, if the ratio of Me_2SiH_2 to C_2F_4 was 5/1, products of type I/II(n=2) / III(x=y=1) were obtained in 83/7/2% yield respectively.

It was observed that the monoaddition product I isolated from this reaction could be transformed into products of type III by further reaction with C_2F_4 (90% yield).



The chain transfer step occurring after the reaction has proceeded for a considerable time can occur by several paths involving either starting material or products containing Si-H bonds. Thus the relative amounts of products of type III produced at any time will vary throughout the reaction, since the concentration of I and Me_3SiH_2 are changing.

Haszeldine devised the following scheme of primary and secondary reactions to account for the product ratios observed.



where (a) chain reaction with the addition of I C_2F_4 unit
(b) chain reaction with the addition of 2 C_2F_4 units
(c) chain reaction with the addition of 3 C_2F_4 units

Observed final yields, mole ratio Me_2SiH_2 to C_2F_4 of 1.5/1:

I	50%	II	n=2	20%	III	x=y=1 7%
			n=3	0.5%		x=1,y=2 8%

The final yields of products indicate that the primary reaction affords I in 50-60% yield and II in 20-30% yield. These yields are then reduced by secondary reactions. The fact that each of the products of type III is produced in approximately the same yield suggests that in each of the secondary reactions the principal products are those resulting from the addition of one C_2F_4 unit in 50% yield and two C_2F_4 units in 25% yield, just as in the primary reaction. If products of type I are desired exclusively however, the use of a large excess of dimethylsilane will promote chain transfer at the expense of propagation as previously noted.

The results of these investigations show that these alkylsilyl radicals are stable enough to facilitate chain transfer from reactive perfluoroalkyl radicals, and suggest a possible route to perfluoroalkylsilanes with high thermal stability.

Russian workers have been active in this field (10,12). A number of halo and alkyl substituted silanes have been added to

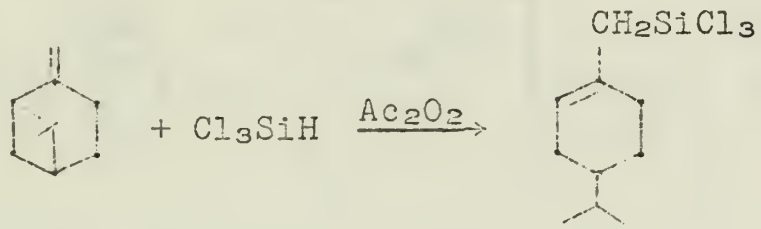
ethylene and propylene to give telomeric products (12). A reaction of this type has been studied in detail by Rochow (19), who investigated the thermal and mercury photosensitized addition of silane to ethylene and acetylene in a circulating system. The products of the ethylene reaction were ethylsilane and diethylsilane, smaller quantities of disilane and trisilane, and a compound tentatively identified as ethyldisilane. The proposed mechanism involves as an initial step the formation of free silyl radicals.

$$SiH_4 \longrightarrow \cdot SiH_3 + H\cdot$$

$$\cdot SiH_3 + C_2H_4 \longrightarrow \cdot CH_2CH_2SiH_3$$

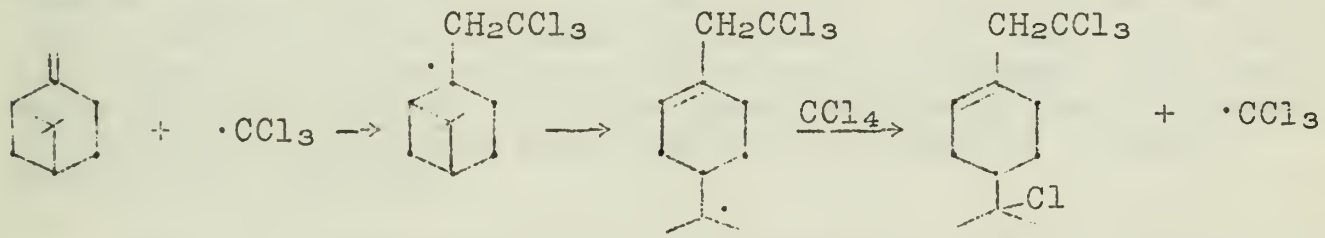
$$\cdot CH_2CH_2SiH_3 + SiH_4 \longrightarrow EtSiH_3 + \cdot SiH_3$$

An interesting reaction between trichlorosilane and β-pinene involving a rearrangement of the terpene skeleton has been reported by Calas and Frainnet (20).



IV V

This structure was proposed on the basis of a strong Raman band at 1674 $cm.^{-1}$, characteristic of the trisubstituted double bond. The authors cite the analogous rearrangement reported by Oldroyd, et al. (21), in the radical addition of CCl_4 to β-pinene as involving a similar mechanism.



VI

The structure proof for the product VI was accomplished by chemical and physical methods including quantitative hydrogenation, ozonolysis, and degradation to the acid VII, with UV spectrum identical to that of authentic material.

Calas and Frainnet have added trichlorosilane to other terpenoid compounds (22).

VII

TRIARYLSILYL RADICALS:

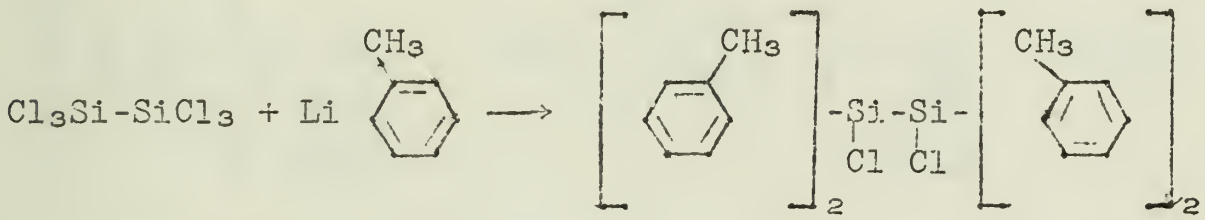
At first sight it might be expected that hexaaryldisilanes, in analogy with hexaarylethanes, might dissociate into rather stable free radicals. Indeed, the

low Si-Si bond energy (45 kcal.) (25) suggests an easier dissociation for the silicon compounds. This expectation has not been realized experimentally (23,24,25,26). Two factors have been considered in rationalizing this fact:

1. Resonance stabilization of the triarylsilyl radicals would involve the contribution of structures containing carbon-silicon double bonds, felt by many to be improbable (27), as between carbon and the other second row elements.

2. The large size of the silicon atoms (Si-Si distance 2.34A) might lead to a lack of steric strain in the disilanes (25) as compared to the ethanes.

Gilman has attacked this problem and concluded that the non-dissociation is not due to a lack of steric strain in at least one of these compounds. When hexachlorodisilane was allowed to react with an excess of ortho-tolyllithium, only 4 of the chlorine atoms were substituted by o-tolyl groups (25):



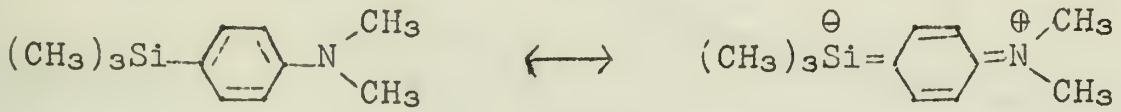
On the other hand, the reaction of tri-o-tolylchlorosilane with sodium produced hexa-o-tolyldisilane (25), while the analogous carbon compound produces free radicals when treated with mercury. Thus the tri-o-tolyl system involves considerable steric strain but will still not produce radicals. The next compound investigated was Hexa-p-biphenyldisilane (25), chosen to maximize the resonance possibilities while minimizing steric crowding at the Si-Si bond. This compound also showed no chemical evidence (i.e., reactivity toward oxygen or iodine) for dissociation. Gilman then attributed the non-dissociation of these compounds to the very small resonance stabilization of the radicals which would be formed. He has not demonstrated, however, that the steric strain present in hexa-o-tolyldisilane is of the same magnitude as that in a highly dissociated compound.

Magnetic susceptibility measurements on 1,1,2-triphenyl-1,2,2, tri-(p-tolyl) disilane (26) confirm the chemical evidence and indicate the absence of free radicals, although the precision of the measurements admittedly cannot rule out a dissociation of as much as 5%.

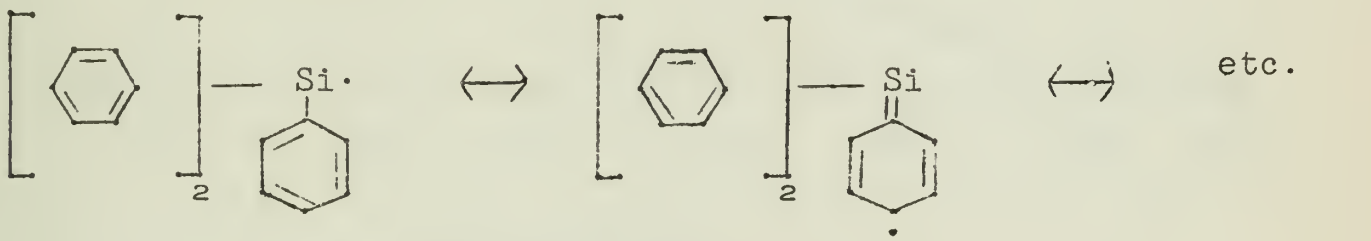
Recent measurements of the dipole moments of several unsymmetrical hexaryldisilanes (28) confirms Gilman's contention that there is some steric strain in these molecules. The dipole moments have been used to calculate a C-Si-C bond angle of 102°, a deformation of about 7.5° from the normal tetrahedral angle.

The non-reactivity of these compounds toward oxygen and an ESR experiment confirmed the previous observation that these compounds were not dissociated into radicals despite this steric strain.

Any valid discussion of resonance in carbon-silicon compounds must differentiate between d-orbital (d_π-p_π) resonance and "ordinary" p_π-p_π resonance. There is considerable evidence for resonance interactions in aromatic silicon compounds (27,29,30,31). For example, Soffer and DeVries (29) measured dipole moments in a series of p-substituted - phenyl trimethylsilanes and showed a definite contribution of resonance structures in certain compounds:



These examples of d_π-p_π resonance can lead to no conclusions as to resonance in silyl-aromatic radicals, for in the latter case resonance would probably involve the unfilled p orbitals of Si rather than d-orbitals:



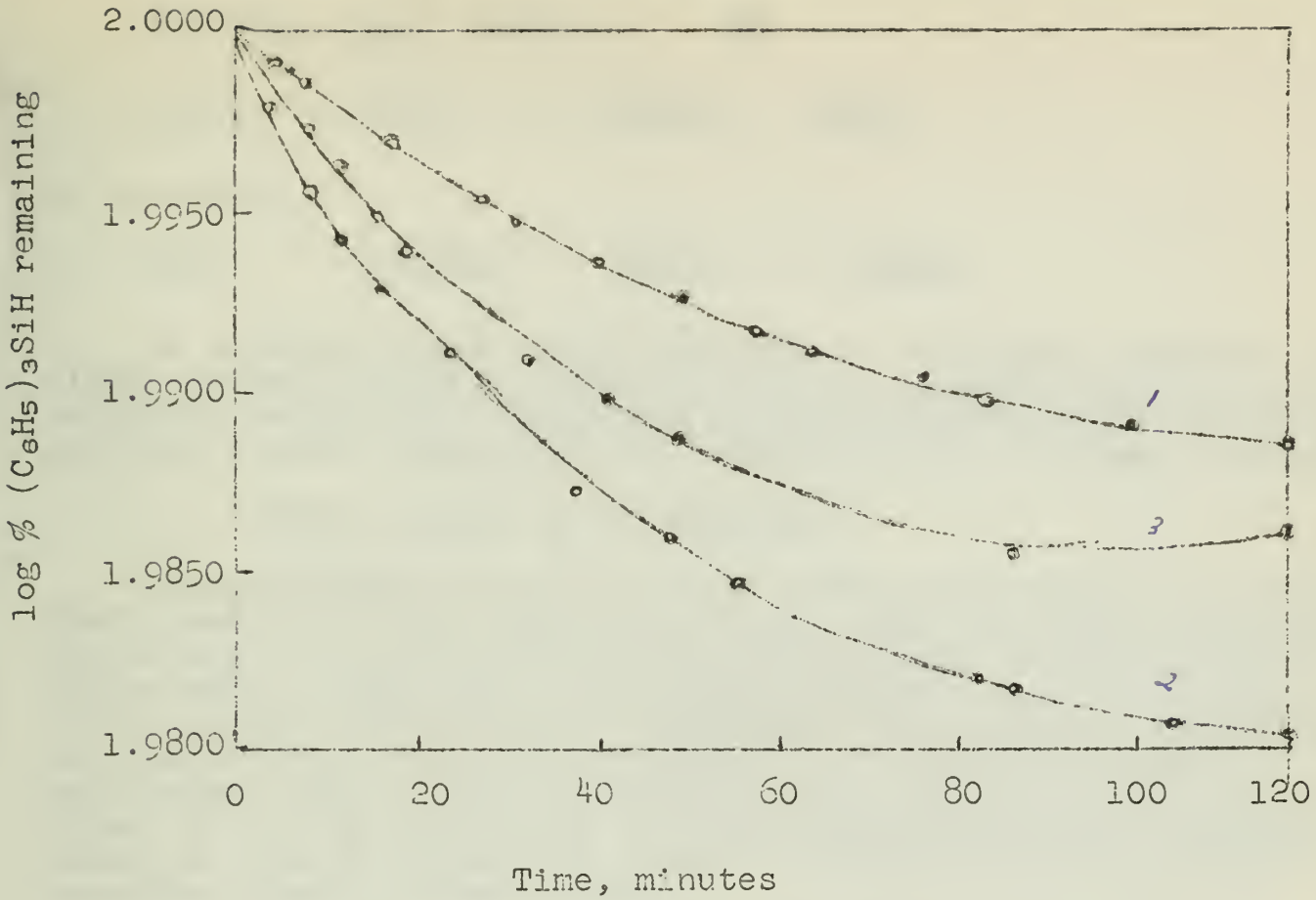
Gilman did not distinguish between these two types of C-Si "double bonds", but π bonding involving p orbitals of silicon has not been observed in compounds, so the qualitative argument against resonance in these radicals may be justified.

The existence of triphenylsilyl radicals as reactive intermediates has been demonstrated in a series of reactions of triphenylsilane (32).

1. OXIDATION

When oxygen was bubbled into a hot benzene solution of triphenylsilane containing a catalytic amount of benzoyl peroxide for 9 hours, triphenylsilanol was isolated in 45% yield. A similar reaction in the absence of peroxide gave a 77% recovery of starting material.

The rate of this oxidation was measured at 62.5°C and 74.4°C. There was an increasing deviation from first order kinetics as the reaction progressed. The deviation became more emphatic in runs at higher temperature and with an increased initial concentration of silane.



RATE OF OXIDATION OF TRIPHENYLSILANE

Run 1, Silane 1.28 M, T = 62.5°

Run 2, Silane 1.28 M, T = 74.4°

Run 3, Silane 2.56 M, T = 74.4°

Azo-bis-isobutyronitrile, 0.101 M in all runs.

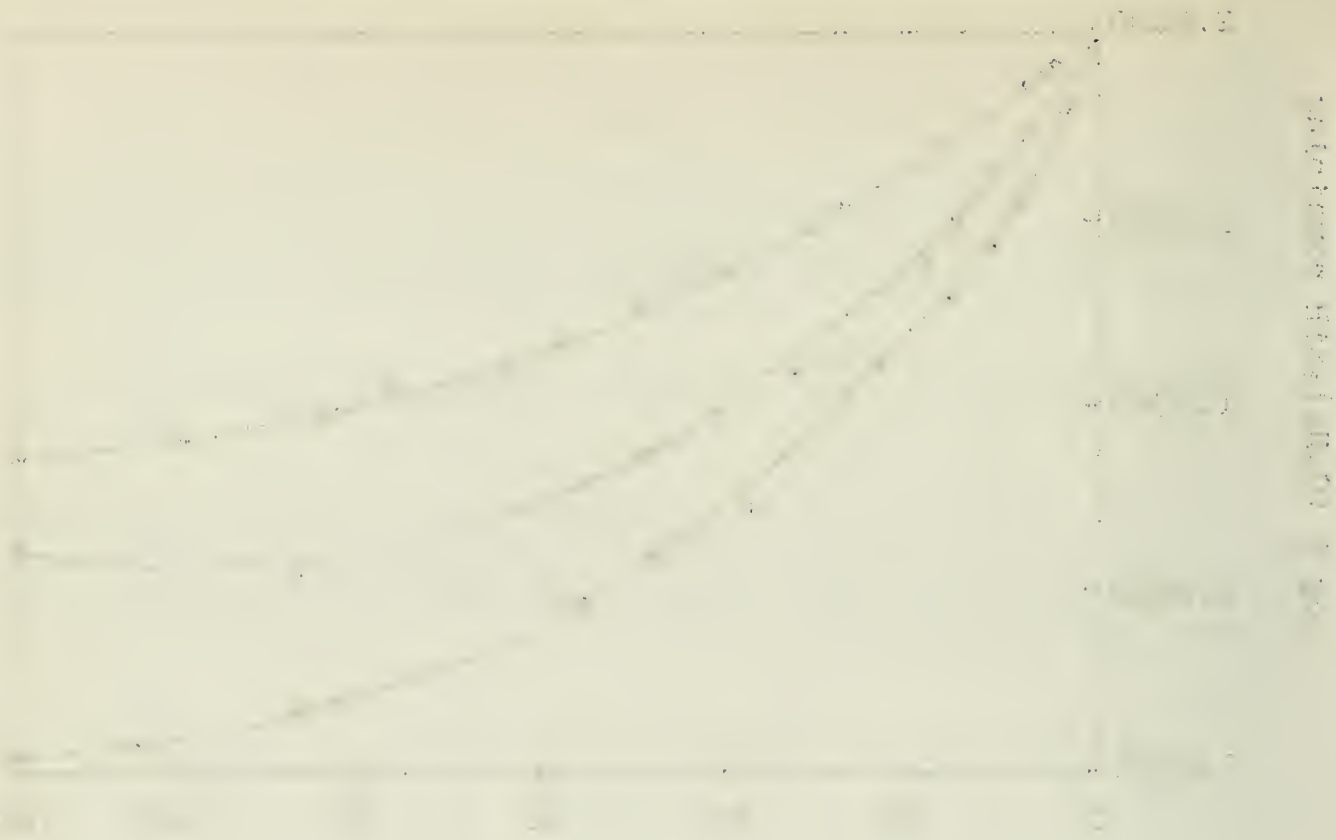
These observations are consistent with the hypothesis that an inhibitor is formed as the reaction progresses, for if we postulate a mechanism analogous to the generally accepted one for low temperature hydrocarbon oxidations (33), the overall process should exhibit a rate equation first order in silane. Such a hypothesis would lead to the conclusion that oxygenated products, such as triphenylsilanol or triphenylsilyl hydroperoxide, can act as radical traps for triphenylsilyl radicals. This reactivity toward oxygen compounds seems to be a characteristic property of silicon radicals.

$$\emptyset_3SiH + R\cdot \longrightarrow RH + \emptyset_3Si\cdot$$

$$\emptyset_3Si\cdot + O_2 \longrightarrow \emptyset_3SiOO\cdot$$

$$\emptyset_3SiOO\cdot + \emptyset_3SiH \longrightarrow \emptyset_3SiOOH + \emptyset_3Si\cdot$$

No species corresponding to a peroxide or hydroperoxide was isolated, the major product being triphenylsilanol. This could be explained by secondary reactions such as:



$$\phi_3SiOOH \xrightarrow{heat} \phi_3SiO\cdot + \cdot OH$$

$$\phi_3SiO\cdot + \phi_3SiH \longrightarrow \phi_3SiOH + \phi_3Si\cdot$$

or possibly:

$$\phi_3Si\cdot + \phi_3SiOOH \longrightarrow \phi_3SiO\cdot + \phi_3SiOH$$

No products illuminating the fate of ·OH were isolated. The single product seems to indicate that the triphenylsiloxy radical undergoes neither the disproportionation characteristic of alkoxy radicals nor the rearrangement characteristic of tritoxy radicals.

2. RADICAL ATTACK ON HALOBENZENES

Chlorobenzene is inert to most carbon free radicals, although phenyl radicals will attack it to form ortho and para chlorobiphenyl. In contrast, triphenylsilyl radicals gererated from triphenylsilane with t-butyl peroxide in chlorobenzene reacted by abstraction of the halogen atom to give a 36% yield of triphenylchlorosilane and traces of o and p chlorobiphenyl. The yield in this unprecedented type of radical reaction with chlorobenzene could be raised to 62% by distilling out the acetone and t-butyl alcohol formed by the decomposition of the 1.2 equivalents of t-butyl peroxide present in the mixture.

This suggests a competition between the volatile materials and chlorobenzene for the triphenylsilyl radicals and confirms the reactivity of these radicals toward oxygen compounds.

Apparent first order rate constants for this reaction were calculated from the equation

$$k_1 = \frac{1}{t} \ln \frac{[\phi_3SiH]_o}{[\phi_3SiH]_o - [\phi_3SiCl]} \quad \text{at } 135^\circ C.$$

The results of the measured rate "constants" were as follows:

t (sec.)	$k_1 \times 10^5$ (sec.$^{-1}$)
1800	5.38
4740	4.66
8050	4.36
12300	3.48
30500	1.65
68400	0.77

The maximum possible rate, calculated as twice the rate of peroxide decomposition at this temperature, is

$7.2\text{-}10.4 \times 10^5$ (sec.$^{-1}$)

Gilman made the assumption of a non-chain mechanism and interpreted this decrease in rate as evidence for the damping effect of oxygen compounds. This simple kinetic analysis, however, can only serve to eliminate a first order rate law for the process, since it reveals nothing about the effect of peroxide concentration on the rate of the reaction.

Similar reactions occurred with fluoro and bromobenzenes. These halogen abstraction reactions are surprising in that they involve breaking of aromatic carbon-halogen bonds and the formation of the unstable phenyl radical.

The absence of the easily detected hexaphenyldisilane in the products points to a high degree of reactivity for triphenylsilyl radicals.

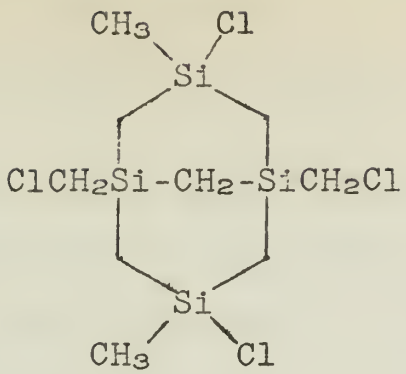
3. CHAIN TRANSFER CONSTANTS

Mayo has derived an equation useful in the determination of chain transfer constants for solvents in the polymerization of styrene (34). The ease of chain transfer for hydrocarbons depends upon the ease of breaking of the C-H bond. Triphenylmethane, for example, is much better than benzene for this purpose. It might be thought that the chain transfer constants for a solvent would furnish some insight into the resonance stabilization of the radicals formed. The difficulty lies in the fact that increasing chain transfer constants generally correlate with increasing frequency factors as well as decreasing activation energy for the transfer reaction. Since the resonance energy of the radicals formed will affect only the activation energy, the chain transfer reaction will not be as sensitive to the resonance stabilization as is the overall reaction.

Curtice, Gilman, and Hammond measured the chain transfer constants for triphenylsilane and triethylsilane at 70°. The ratio of the chain transfer constants was 13.7 to 1, implying a lower free energy of activation for the triphenylsilane. This could be attributed to either a difference in resonance stabilization of the radicals produced, or to an inductive weakening of the Si-H bond by the three phenyl rings. Because of the uncertainty as to frequency factors it is impossible to estimate the resonance stabilization. Both silanes, however, are better chain transfer agents than their hydrocarbon analogs, which may indicate the facility of this step is due to a lower Si-H bond energy rather than resonance.

THERMAL AND ELECTRICAL DECOMPOSITION OF SILANES

The thermal stabilities of a variety of organosilanes have been examined by Fritz (35-37). The products of the thermal decomposition of trimethylchlorosilane at 800° (37) were hydrogen, methane, ethylene, ethane, silane and simple methylsilanes, together with a colorless, crystalline substance, soluble in organic solvents and subliming at 200-220°. It has a molecular formula of $Si_4C_9Cl_4H_{20}$ (M.W. 388, Calc. 382) with no Si-H or Si-Si bonds, and only half the chlorine is bound to silicon. No linear compound can fit all of these facts, and the cyclic structure VIII was proposed on the basis of its chemical properties and molecular models.



VIII

Similar compounds were obtained from tetramethylsilane and methyltrichlorosilane. Several steps involving unprecedented radical reactions seem to invalidate the mechanism proposed to account for the products (36).

Andreev has published a series of papers describing the decomposition of methyltrichlorosilane (38), the reaction of methyltrichlorosilane with hydrogen (39), and the reaction of silicon tetrachloride with cyclohexane (40) under the influence of a silent electric discharge. In each case a mechanism involving silyl radicals was proposed. One of the steps in the reaction with cyclohexane is proposed to be a radical displacement on silicon:

$$C_6H_{12} \longrightarrow C_6H_{11}\cdot + H\cdot$$

$$C_6H_{11}\cdot + SiCl_4 \longrightarrow C_6H_{11}SiCl_3 + Cl\cdot$$

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DIBENZENECHROMIUM AND RELATED COMPOUNDS

Reported by W. H. Pittman January 9, 1958

INTRODUCTION

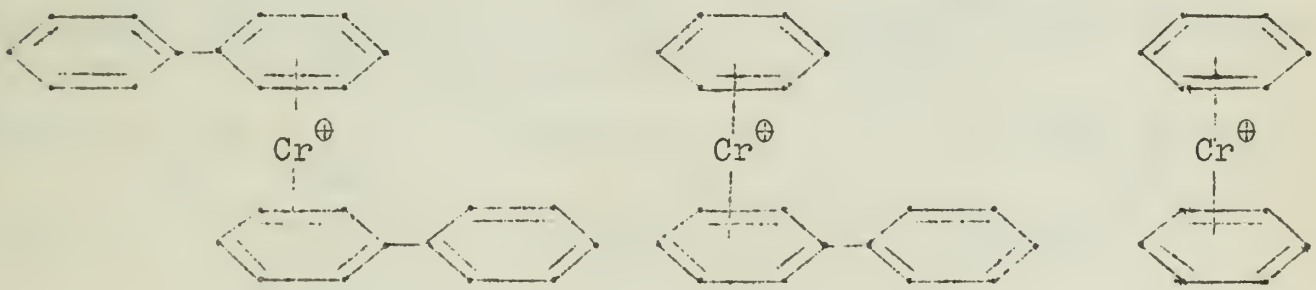
With the synthesis of ferrocene in 1951, an entirely new class of organometallic compounds was brought to light. These are the so-called "sandwich" compounds; they are, in general, composed of two aromatic rings bound to a transition metal atom, and are notable chiefly because of the existence of a non-classical bond linking the metal atom with the organic species.

The "sandwich" compounds can be conveniently divided into two groups: first, the cyclopentadienyl-metal compounds, and second, those in which the organic species is an aromatic hydrocarbon. It is with the second of these groups that this seminar is concerned. The most thoroughly studied of these compounds are those containing chromium; therefore, the bulk of this seminar will deal with the organochromium compounds.

HISTORICAL

The earlier investigations in organochromium compounds have been summarized in a review by Cotton (1). This work will be treated only briefly here.

Hein and his co-workers prepared the first organochromium compounds in 1919, by reacting anhydrous chromic chloride with phenylmagnesium bromide (2). They were able to isolate three series of compounds from the mixture thus formed; these were later identified, by synthetic (3,4,5), chromatographic (6,7), and degradative methods (8,9), as salts of two cations: bis-biphenylchromium (I) (A) and benzenebiphenylchromium (I) (B). It was later found (3,7) that the mixture also contained the dibenzenechromium (I) ion (C); this ion had been missed originally because of the high water-solubility of its salts.



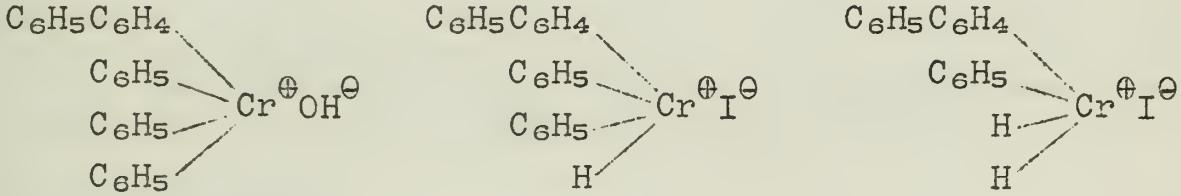
A B C

At the time of the isolation of these compounds, however, the above structures were not suspected. Hein thought the substances he had obtained were "pentaphenylchromium hydroxide" (10,11), "tetraphenylchromium iodide" (12,13,14), and "triphenylchromium iodide" (15), containing chromium in the +6, +5, and +4 oxidation states, respectively, with the phenyl groups attached to the chromium by covalent bonds. The following facts were in opposition to this formulation: (a) All the compounds were orange-brown in color and absorbed at about 350 mμ in the ultra-

violet (8); (b) they were all found, by magnetic susceptibility measurements (16), to contain one unpaired electron; (c) attempts to prepare "pentaphenylchromium" salts by neutralization of "pentaphenylchromium hydroxide" resulted, in almost all cases, in the loss of one phenyl group and the formation of the corresponding "tetraphenylchromium" salt, but no hydrogen was given off as would be expected according to the following equation (11):

$$(C_6H_5)_5CrOH + HX \longrightarrow (C_6H_5)_4CrX + C_6H_5OH + (H)$$

On the basis of magnetic susceptibility measurements on the compounds prepared by Hein, Klemm and Neuber (16) suggested the following formulations for these compounds, all involving pentavalent chromium.

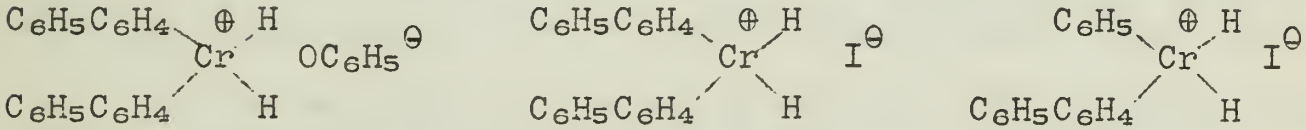


These structures were subsequently disproved on the basis of degradative and isotope studies described below.

STRUCTURE OF ORGANOCHROMIUM COMPOUNDS

Zeiss and Tsutsui (8) found that "pentaphenylchromium hydroxide" gave two mole-equivalents of biphenyl and one of phenol upon reduction with lithium aluminum hydride. Similar reduction of "tetraphenylchromium iodide" afforded two mole-equivalents of biphenyl, and "triphenylchromium iodide" yielded one mole-equivalent of biphenyl and one of benzene. Reduction of diphenylmercury under similar conditions gave only benzene. These results were considered to be proof of the invalidity of Hein's structural postulations. In particular, it now appeared that "pentaphenylchromium hydroxide" was actually "tetraphenylchromium phenolate".

Next the Klemm-Neuber formulas were examined (8). These structures were modified as follows, to account for the products obtained by lithium aluminum hydride reduction:



Reduction of "tetraphenylchromium iodide" with lithium aluminum hydride, followed by hydrolysis with deuterium oxide, afforded biphenyl containing no deuterium. Reduction with lithium aluminum deuteride gave biphenyl containing five mole per cent deuterium. Under the same conditions, biphenyl itself was not deuterated by lithium aluminum deuteride. Thus, it was shown that biphenyl was formed no later than the reaction of the organochromium compound with lithium aluminum hydride; however, on the basis of the Klemm-Neuber structure, the biphenyl would be expected to contain ten mole per cent deuterium. When "triphenylchromium iodide" was reduced with $LiAlD_4$, the biphenyl obtained contained only 6.7% deuterium, rather than 10% as expected. (The deuterium

content of the benzene was not measured.) Thus, the structures proposed by Klemm and Neuber were rendered extremely unlikely.

The correct formulations for the organochromium compounds were suggested by Onsager (8) in 1955. It is now known that Hein's "pentaphenylchromium hydroxide", "tetraphenylchromium iodide", and "triphenylchromium iodide" are actually bis-biphenylchromium (I) phenolate, bis-biphenylchromium (I) iodide, and benzenebiphenylchromium (I) iodide, respectively.

The results of the lithium aluminum deuteride studies have not yet been satisfactorily explained. Zeiss and Tsutsui (8) have suggested that attack of a deuteride ion on one of the aromatic rings of the organochromium compound causes collapse of the compound and expulsion of a hydride ion. However, it is not clear, on the basis of what is now known about these compounds, why they should be attacked by a deuteride ion at all. Also, the deuterium content of the products of the reduction of benzenebiphenylchromium (I) iodide cannot be reconciled with its structure.

Electronic Structure

In considering the possible electronic structures for dibenzenechromium, it is necessary to compare this compound with ferrocene, since the latter has been more extensively studied. Fischer has suggested (17,18) that both compounds are "penetration complexes", in which each of two cyclopentadienyl anions (or benzene molecules) donates six π electrons to the empty orbitals of the ferrous ion (or chromium atom), giving the metal species a filled shell corresponding to the configuration of krypton. This theory has been attacked for the following reasons (19):

(a) The geometry of ferrocene does not correspond to an octahedral configuration for the complex, as would be expected if six electron pairs are coordinated.

(b) The donation of all the π electrons should lead to loss of aromatic character, but ferrocene is known to undergo aromatic reactions readily.

(c) This type of bond would cause a large negative charge to build up on the iron atom and a large positive charge on the rings, but the rings have been shown to be electrically almost neutral.

(d) The magnetic properties of certain other cyclopentadienyl metal compounds, particularly $(C_5H_5)_2Ni$, are not correctly predicted by the "penetration complex" hypothesis.

(e) Many cyclopentadienyl metal "sandwich" compounds are known in which the rare gas configuration could not be attained in this way.

Several workers have considered the bonding in ferrocene from a molecular orbital standpoint. Dunitz and Orgel (20) and Moffitt (21) have, perhaps, presented the most reasonable theories. Jaffé's treatment (22) is weak in that it considers all the π electrons of the rings to be involved in bonding with the metal atom (in this respect it is similar to Fischer's "penetration complex" theory); however, Linnett (23) has published an article purporting to show

that Jaffé's work is not really as different from Moffitt's as it seems. These theories will not be treated in detail here. Rather, a description of the more important features of the molecular orbital treatment of ferrocene will be given, and dibenzene-chromium will then be considered from the same standpoint.

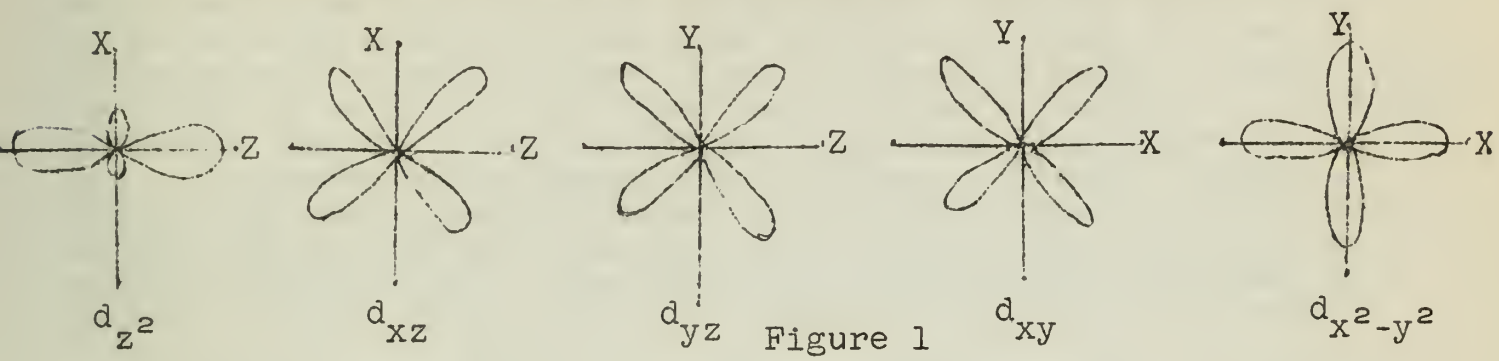


Figure 1

The geometries of the five 3d orbitals of the iron (or chromium) atom are shown in Figure 1. It will be seen that d_{xz} can be converted into d_{yz} by rotating it 90° about the z axis. Now let two cyclopentadienyl radicals approach the metal atom from opposite directions along the z axis. Under their influence, two doughnut-shaped orbitals, perpendicular to the z axis, are formed from the d_{xz} and d_{yz} orbitals. These new orbitals may be represented by d_{+1} and d_{-1}. The d_{xy}, d_{z^2}, and $d_{x^2-y^2}$ orbitals become fully occupied by six of iron's eight 3d and 4s electrons; the other two electrons move into the d_{+1} and d_{-1} orbitals, respectively. Overlap of the d_{+1} and d_{-1} orbitals with two singly-occupied doughnut-shaped molecular orbitals of the cyclopentadienyl radicals forms two bonding molecular orbitals, each containing two electrons, and two empty antibonding molecular orbitals. The resulting compound can be considered as resulting from two cyclopentadienyl radicals and one iron atom, or from two cyclopentadienyl anions and one ferrous ion.

The chromium atom, being isoelectronic with the ferrous ion, contains six electrons in the 3d and 4s orbitals. If these electrons pair up in the d_{xy}, d_{z^2}, and $d_{x^2-y^2}$ orbitals under the influence of two approaching benzene rings, two electrons from each ring can be donated to a bonding M. O. formed from the d_{+1} or d_{-1} orbital and one of the benzene M. O.'s. The bonding is essentially a donor-acceptor type; however, the electron cloud of the benzene is not perturbed enough to cause loss of much delocalization energy.

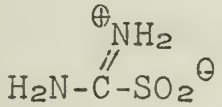
SYNTHESIS OF ORGANOCHROMIUM COMPOUNDS

Compounds A, B, and C were obtained by Hein (2) as a mixture through the reaction of phenylmagnesium bromide with anhydrous chromic chloride. Separation was effected in various ways, the most efficient of which involved precipitation of benzenebiphenyl-chromium (I) anthranilate (the other anthranilates apparently are quite soluble in water) (24).

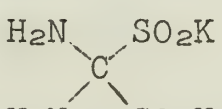
The "reducing Friedel-Crafts method", developed by Fischer in 1955 (17), appears to be the best method for obtaining organochromium compounds in relatively good yield. As described for the preparation of dibenzenechromium salts (25), this method consists in heating equimolar quantities of anhydrous chromic chloride, aluminum chloride, and powdered aluminum with an excess of benzene in a sealed tube. The reaction mixture is then hydrolyzed with aqueous methanol and the desired salt is precipitated by treating with the appropriate acid or salt solution. The same procedure has been used to prepare bis-biphenylchromium (I) iodide (4). Compounds of chromium with toluene, p-xylene, tetralin, mesitylene, and hexamethylbenzene have been prepared by the same method (25,26), as have similar compounds of other transition metals (27,28,29,30). The following stoichiometry has been proposed (27) for the reaction of chromic chloride with benzene:

$$3CrCl_3 + 2Al + AlCl_3 + 6C_6H_6 \longrightarrow 3[(C_6H_6)_2Cr]^+ + 3[AlCl_4]^-$$

Reduction of organochromium salts can be accomplished by several methods. Hein obtained "triphenylchromium" and "tetraphenylchromium" by reducing the corresponding iodide by electrolysis in liquid ammonia (31,32). Fischer used sodium dithionite ($Na_2S_2O_4$) to prepare dibenzenechromium from dibenzenechromium (I) hydroxide (25). For the reduction of bis-biphenylchromium (I) iodide (4), and also in the preparation of dibenzenemolybdenum (28), formamidinesulfinic acid (D) (33) or potassium diaminomethanedisulfinate (E) were used. Hypophosphorous acid (5) has also been employed as a reducing agent in the preparation of bis-biphenylchromium.



D



E

Mechanism of the Formation of "Polyphenylchromium" Salts

Several proposals have been made concerning the mechanism of the reaction of phenylmagnesium bromide with chromic chloride. The chief interest has, of course, been to postulate a scheme which would correctly predict the formation of all the compounds found in the reaction mixture.

Two possible schemes have been suggested by Hein (34) for the formation of bis-biphenylchromium halide, one being an initial formation of tetraphenylchromium halide followed by an intramolecular rearrangement to produce bis-biphenylchromium (I) halide:

(a) $3CrX_3 + 4C_6H_5MgX \longrightarrow (C_6H_5)_4CrX + 2CrX_2 + 4MgX_2$

1.

(b) $(C_6H_5)_4CrX \longrightarrow (C_6H_5C_6H_5)_2CrX$

The other mechanism involves a reduction of chromium (III) to chromium (I) by the Grignard reagent, followed by reaction of the chromium (I) with biphenyl produced during the oxidation-reduction process:

2. (a) $2C_6H_5MgX + CrX_3 \longrightarrow C_6H_5C_6H_5 + CrX + 2MgX_2$

(b) $2C_6H_5C_6H_5 + CrX \longrightarrow (C_6H_5C_6H_5)_2CrX$

Formation of benzenebiphenylchromium and dibenzenechromium compounds according to Hein, is caused by exchange of benzene for one or both biphenyls in bis-biphenylchromium (I) halide, the benzene being formed by the action of traces of water on the phenylmagnesium bromide.

Hein claims there is evidence for the presence of CrX_2 and CrX in the reaction mixture, but the evidence was not given. However, if scheme 2 is correct, the same compounds should be obtained by reducing CrX_3 with another Grignard reagent, e.g. C_2H_5MgX, in the presence of biphenyl. Hein tried this method and did not succeed, although some chromium (I) was found to be present through precipitation by α,α'-dipyridyl as the complex salt $[(dipy)_3Cr]X$.

Both of these mechanisms seem questionable, since it does not seem possible that enough water could find its way into the reaction mixture, in all cases, to form appreciable quantities of benzenebiphenylchromium and dibenzenechromium salts. Scheme 1 suffers from the additional handicap of involving a very unlikely chromium (V) intermediate.

Zeiss and Herwig (3,5) have proposed a third scheme, also involving an oxidation-reduction followed by a complexing step:

3. (a) $2C_6H_5MgX + CrX_3 \longrightarrow C_6H_5C_6H_5 + CrX + 2MgX_2$

(b) $2C_6H_5MgX + CrX \longrightarrow \underset{F}{(C_6H_5MgX)_2CrX}$

(c) $F + C_6H_5MgX + CrX_3 \longrightarrow \underset{G}{(C_6H_5MgX)(C_6H_5C_6H_5)CrX} + CrX + 2MgX_2$

Alternatively, the Grignard reagent might react with the chromic halide to produce an organochromium intermediate, as follows:

(a'$_1$) $C_6H_5MgX + CrX_3 \longrightarrow C_6H_5CrX_2 + MgX_2$

(a'$_2$) $2C_6H_5CrX_2 \longrightarrow C_6H_5C_6H_5 + CrX + CrX_3$

(b') $2C_6H_5CrX_2 + CrX \longrightarrow \underset{F'}{(C_6H_5CrX_2)_2CrX}$

(c') $F' + C_6H_5CrX_2 \longrightarrow \underset{G'}{(C_6H_5CrX_2)(C_6H_5C_6H_5)CrX} + CrX + CrX_3$

Hydrolysis of intermediate F (or F') would give dibenzenechromium (I) halide, while hydrolysis of G (or G') would give benzenebiphenylchromium (I) halide. A repetition of step (c) or (c'), starting with intermediate G or G', would produce a third intermediate which would be converted by hydrolysis to bis-biphenylchromium (I) halide. An alternative series for the formation of G and subsequent products is as follows:

(a) $2C_6H_5MgX + CrX_3 \longrightarrow (C_6H_5)_2CrX + 2MgX_2$

(b) $(C_6H_5)_2CrX \longrightarrow (C_6H_5C_6H_5)CrX$

3a.

(c) $(C_6H_5C_6H_5)CrX + C_6H_5MgX \longrightarrow G \xrightarrow{H_2O} (C_6H_6)(C_6H_5C_6H_5)CrX$

(d) $(C_6H_5C_6H_5)CrX + C_6H_5C_6H_5 \longrightarrow (C_6H_5C_6H_5)_2CrX$

Scheme 3 might be considered more reasonable than 3a, because the latter involves a monoaromatic-chromium system, for which there seems to be no theoretical or experimental evidence.

Carbonation of the reaction mixture from the Hein reaction, followed by hydrolysis with dilute sodium hydroxide and precipitation as the tetraphenylborate, afforded a product which showed strong absorption in the carboxylate region of the infrared. Also, when the original mixture was hydrolyzed with deuterium oxide and worked up, the resulting benzenebiphenylchromium (I) tetraphenylborate had the typical C-D band at 2260 cm^{-1}, while the bis-biphenylchromium (I) salt had no such band. Thus, some evidence is furnished for an intermediate such as G.

PHYSICAL PROPERTIES

The monovalent organochromium salts which are most easily isolated (due to their insolubility in water) are the reineckates, tetraphenylborates, and iodides. In general they are crystalline solids, ranging from yellow to dark brown in color (4,7,17). Magnetic susceptibility measurements (4,16,17,35,36) show the presence of one unpaired electron in the cation in each case.

Dibenzenechromium and analogous neutral organochromium compounds are brown crystalline solids (4,17). They are all diamagnetic (4,17,35,36) and have dipole moments of zero (4,17,37, 38).

On the basis of dipole moment results, it has been generally assumed that substituted dibenzenechromiums exist in the trans configuration, as in Figure 2 (3,4). However, Zeiss and Herwig (3) have asserted that bis-biphenylchromium may have the configuration shown in Figure 3. Since this orientation is hardly possible for the alkyl-substituted analogs, the trans structure seems more likly at present.

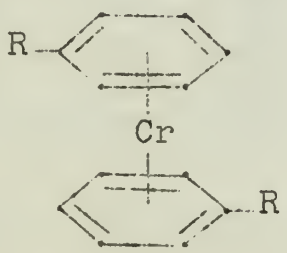


Figure 2

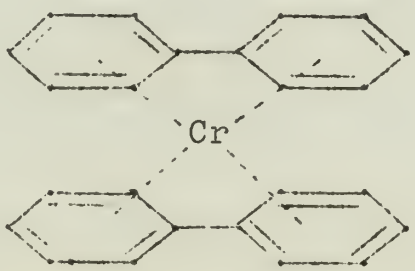


Figure 3

X-ray diffraction studies on both dibenzenechromium (39) and bis-biphenylchromium (4) confirm the "sandwich" structure. Evidence concerning rotation of the rings, however, appears

to be contradictory. X-ray evidence (39) shows that the rings are superimposed, as in Figure 2, in the crystalline state. Fischer suggests that free rotation of the rings may be possible in non-crystalline phases. But recent broad line nuclear magnetic resonance studies (40), apparently made on the solid material (though the authors are not explicit on this point), have been interpreted as showing that there is actually free rotation in the crystalline material at temperatures above -79°C. Further work along these lines may be expected to clear up the present uncertainty as to rotational freedom of the rings.

Carbon-carbon bond distances in dibenzenechromium were found to be 1.38±0.05 A (39), about the same as in benzene.

Recently the method of electron spin resonance has been applied to the dibenzenechromium (I) cation (41). The spectrum confirms a deep-seated interaction between the π electrons of the benzene and the d-orbitals of the chromium. Also, a consideration of the hyperfine structure indicates that the unpaired electron interacts with the hydrogens on the benzene rings, as well as with the chromium atom.

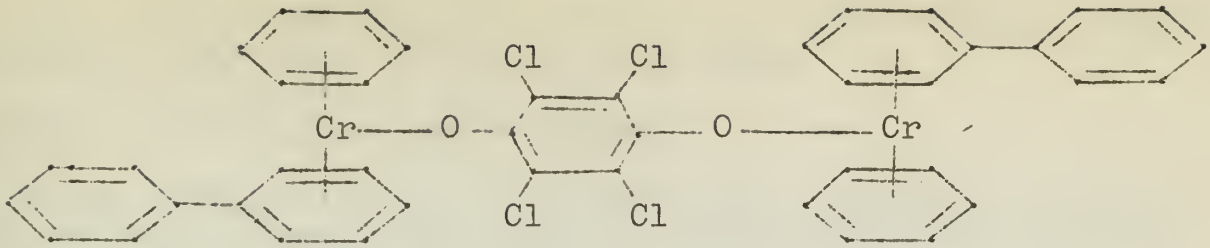
CHEMICAL PROPERTIES

Dibenzenechromium and its analogs are soluble in organic solvents, but not in water. They are, however, stable toward water and also toward dilute acids and bases. Thermally, they are also quite stable; dibenzenechromium does not decompose below about 300° in the absence of air (17,35). The neutral compounds are easily oxidized to the corresponding cations; iodine, in ether solution, has been used for this purpose (24). Oxidation by air takes place quite readily (17).

The organochromium cations are also stable toward water and aqueous acids and bases (17,35). Dibenzenechromium (I) hydroxide and analogous compounds are strong bases (13,17). Methods for reducing the cations have already been described.

A comparison of the ease of oxidation of dibenzenechromium and ferrocene is interesting. Ferrocene is easily oxidized to the ferricinium ion by air in the presence of acids, by halogens, by ferric chloride, or by ceric sulfate (42). The ion is easily reduced by stannous chloride (42). No report has been made of the action of these reagents on the corresponding organochromium compounds. From a qualitative standpoint, however, it appears that the two systems behave similarly with respect to oxidation and reduction. The electrode potential of the ferrocene-ferricinium system has been found to be -0.59 volt (42); that of the dibenzenechromium(0)-dibenzenechromium (I) system has not yet been reported.

The organochromium cations, because of their unpaired electron, have some "radical" character. Benzenebiphenylchromium reacts with chloranil to form a yellow-orange compound for which the following structure has been suggested (24):



Sodium tetraphenylborate decomposes this compound with the precipitation of benzenebiphenylchromium (I) tetraphenylborate.

An interesting compound with the formula $(C_6H_6)_2Cr_2(C_5H_5)(CO)_3$ has been synthesized by Fischer and Kogler (43) by reacting dibenzenechromium (I) hydroxide with $Na[(C_5H_5)Cr(CO)_3]$ (prepared from dicyclopentadienylchromium, carbon monoxide, and NaOH) in aqueous solution. Magnetic susceptibility measurements, which show one unpaired electron, suggest the salt structure $[(C_6H_6)_2Cr]^+$ $[(C_5H_5)Cr(CO)_3]^-$, where the chromium in the anion is apparently in the zero oxidation state.

Aromatic Character

Fritz and Fischer (44) attempted several aromatic substitution reactions with ditoluenechromium, but in no case did they obtain the expected substituted organochromium compounds. Friedel-Crafts reactions with acetyl chloride and benzoyl chloride gave as chief products only the ortho- and para-acylated toluenes. Mercuration attempts with mercuric salts resulted in oxidation of the compound to the $(C_6H_5CH_3)_2Cr^+$ ion. When mercuration of the ion was attempted, decomposition took place. Metalation with n-butyllithium was also unsuccessful. More vigorous reactions, such as nitration and sulfonation, led to oxidation and decomposition. Radical and nucleophilic substitution reactions also caused decomposition of the compound.

A possible explanation for the failure of ditoluenechromium to undergo electrophilic substitution, as contrasted with ferrocene which undergoes such reactions readily, can be provided by considering the transition states involved. It seems reasonable to assume that a transition state of the type usually associated with aromatic substitution reactions is actually attained by both ferrocene and dibenzenechromium. In ferrocene, the net negative charge on the cyclopentadienyl ring tends to stabilize the positive charge associated with the attacking group. However, no such negative charge exists in organochromium compounds; the ring has, if anything, a slight positive charge because of the donor-acceptor character of the bond with the metal atom. The additional positive charge brought up by the reagent causes the molecule to decompose, giving the substituted toluene derivative and other products. This explains the recovery of acylated toluenes from the Friedel-Crafts reaction mixture.

The failure of radical and nucleophilic substitution reactions is more difficult to explain. Further study of them might be worthwhile.

The above hypothesis presupposes that substitution takes place before the organochromium compound decomposes. Whether this is

true has not been determined; however, it seems likely considering the general stability of dibenzenechromium.

COMPOUNDS OF OTHER TRANSITION METALS

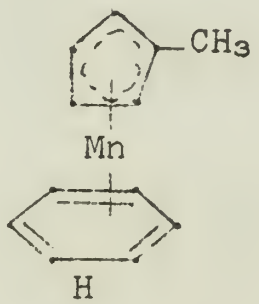
Several other transition metals form compounds of the dibenzenechromium type. The reducing Friedel-Crafts method of synthesis has been used by Fischer (27,28,29,30) for most of these compounds. Preparative details and a few physical properties for compounds obtained by this method are given in Table 1.

Fischer was unable to obtain a benzene analog of the dimesityleneiron (II) cation (30). This fact was taken as an indication that the most stable compounds of this type are formed from aromatic species which are threefold-symmetrically substituted (30,44). Tsutsui and Zeiss disagreed with this theory (45). They prepared compounds of iron with benzene, toluene, xylene, mesitylene, durene, and hexamethylbenzene (no preparative procedure was given) and tested their relative stability by treating with KSCN, $K_4[Fe(CN)_6]$, and $K_3[Fe(CN)_6]$. They found that the stability of the organoiron compounds increased with increasing substitution on the benzene rings.

The following proposals were made on the basis of these results: (a) Decomposition of aqueous solutions of the organoiron compounds involves an oxidation-reduction process; (b) the relative stability of the compounds depends in part upon the amount of steric blocking of the approach to the iron of the attacking reagent, and also in part on the inductive release of electrons to the π bonds by the substituent groups.

Recently the first mixed "sandwich" compound belonging to both the cyclopentadienyl and benzene series was reported by Coffield, Sandel, and Closson (46). They prepared methylcyclopentadienyl manganese benzene (H) by the following series of reactions:

$$NaC_5H_4CH_3 + MnCl_2 \longrightarrow (C_5H_4CH_3)MnCl \xrightarrow[H_2O]{C_6H_5MgBr} (C_5H_4CH_3)Mn(C_6H_6)$$



The compound, the first such complex reported for manganese, consists of ruby-red crystals, m.p. 116-118°. It is relatively stable to air and is thermally stable below its melting point.

TABLE I

"SANDWICH" COMPOUNDS OF NEUTRAL AROMATIC SPECIES WITH TRANSITION METALS OTHER THAN CHROMIUM

Compound*	Starting material: Halide	Starting material: Aromatic H.C.	Reducing agent	Physical properties	Reference
$(C_6H_6)_2Mo$	$MoCl_5$	Benzene	Potassium diamino-methanedisulfinate or alkaline dis-proportionation	Green crystalline solid: diamagnetic	28
$[C_6H_3(CH_3)_3]_2Mo$	No preparative details given.			Green volatile compound	28
$(C_6H_6)_2W$	No details given.				27
$(C_6H_6)_2V$, $[C_6H_3(CH_3)_3]_2V$	VCl_4	Benzene, Mesitylene	Aqueous dis-proportionation	Dark red-brown solids: contain one unpaired electron	27
$(C_6H_6)_2Re^+$, $[C_6H_3(CH_3)_3]_2Re^+$	$ReCl_5$	Benzene, Mesitylene	----------	Pale yellow solutions: diamagnetic	29
$[C_6H_3(CH_3)_3]_2Fe^{+2}$	$FeBr_2$	Mesitylene	----------	Deep orange solution: diamagnetic	30

*Where neutral compound is shown, it was obtained by reducing univalent cation with reducing agent shown. Where ion is shown, neutral compound was not obtained.

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MICROBIOLOGICAL TRANSFORMATIONS OF STEROIDS

Reported by W. J. Lennarz January 13, 1958

INTRODUCTION

Twenty years ago Mamoli and co-workers published their discoveries concerning the microbiological reduction of certain steroids by yeast cells (1). They continued investigations in this field but, with the exception of a small number of other investigators, little interest was aroused. Over ten years later, Hench (2) demonstrated the clinical effects of cortisone and hydrocortisone in the treatment of rheumatoid arthritis. Then, in 1952, Peterson (3) reported the discovery of molds that could hydroxylate progesterone, thus producing 11α-hydroxyprogesterone. By this time the now-classical synthesis of cortisone from deoxycholic acid by Sarett (4), and the total syntheses by Sarett (5), Woodward (6), and others had been accomplished and the search for shorter synthetic routes was on; thus the microbiological approach was brought to the fore.

Interest in this field has been sustained up to the present time, and although a great deal of the research has been directed toward the microbiological synthesis of the cortical hormones, a large amount of general information on steroidal transformations has been accumulated.

The early work has been summarized by Fischer (7). Since that time numerous reviews covering various aspects of microbial transformations have appeared (8)(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19), and two comprehensive reviews tabulating all known microbial transformations of various steroids have been published (20)(21). The latter, by Eppstein and co-workers, is an excellent reference source when one wishes information on a specific type of transformation on a particular steroid, while the former has a convenient tabular classification of individual microorganisms and the transformations they have accomplished.

The aim of this seminar is to discuss the general types of steroidal transformations that can be accomplished by microbial action. Particular emphasis will be placed on the practical aspects of this synthetic technique and its applicability to steroid chemistry in general. Recent work that has been done towards the elucidation of the mechanism of microbial transformations will be discussed.

THE MICROORGANISM

The large number of microorganisms that have been used to accomplish steroidal transformation fall into two main groups; the bacteria and the fungi, which include yeasts and molds.

Enzymes produced by the microorganisms are, of course, responsible for the transformations, and in several cases these enzymes have been isolated (see below). Most enzymes are made up of a high molecular weight protein to which is attached a non-protein moiety. This moiety may be diphosphopyridine nucleotide, riboflavin, protoporphyrin, etc., and is usually intimately involved in the enzymatic reaction. The enzyme reacts with the substrate to form one or more intermediate enzyme-substrate complexes. Due to the high degree of stereospecificity of enzyme-catalyzed reactions, it is

thought that the substrate must become aligned to a definite position on the surface of the enzyme; the enzyme may be thought of as a 'template'. The complex thus formed then 'decomposes', yielding the enzyme and the product.

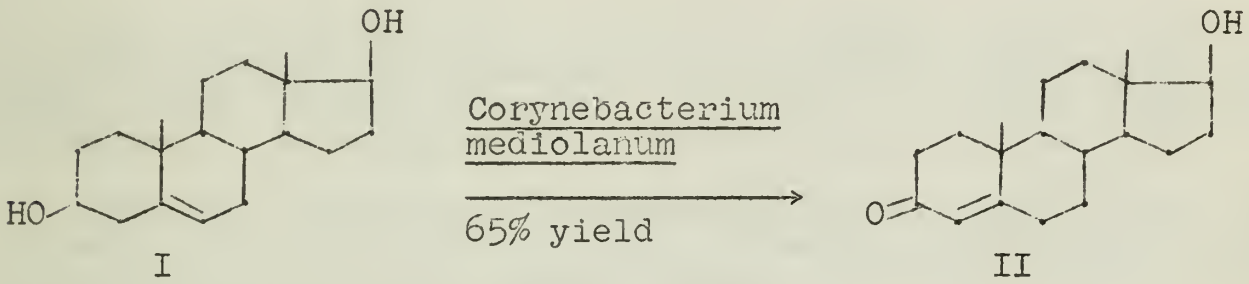
GENERAL TYPES OF TRANSFORMATIONS

The very large number of different steroidal reactions that have been accomplished by microorganisms may be classified in the following manner:

1. Oxidation of hydroxyl groups and reduction of ketones
2. Reduction and formation of nuclear double bonds
3. Side chain cleavage and ring cleavage
4. Hydroxylation
5. Ester hydrolysis
6. Epoxidation

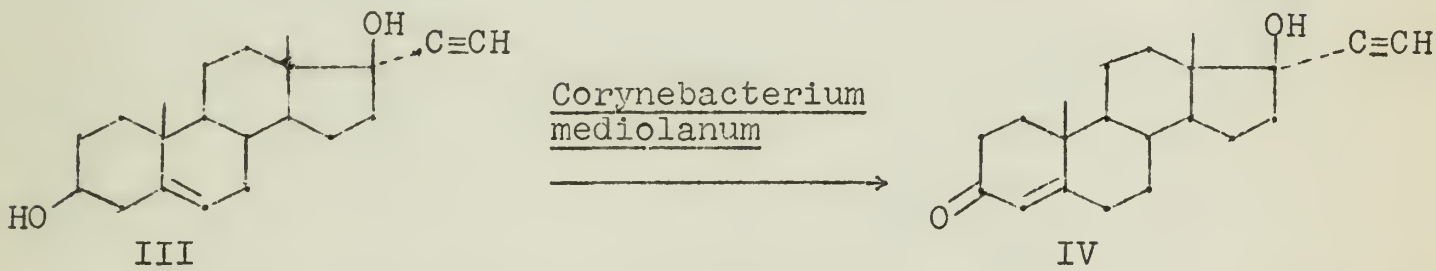
I OXIDATION OF HYDROXYL GROUPS AND REDUCTION OF KETONES

In general, the selective or complete oxidation of the 3β- or 17β-hydroxyl groups in the androgen-type steroids is readily accomplished by several species of bacteria and yeast. The oxidation of the 3β-hydroxyl group of Δ^5-androstene-3β, 17β-diol (I) is illustrative (22)(23).



I II

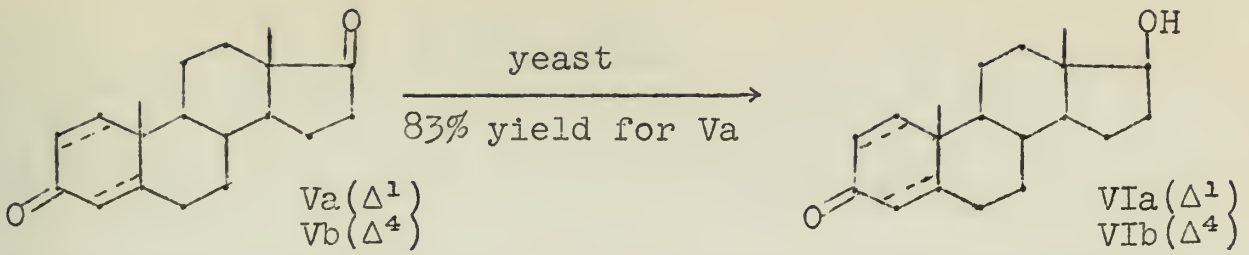
A wide variety of compounds may be oxidized in this manner, as illustrated by the oxidation of the ethynyl derivative III (24).



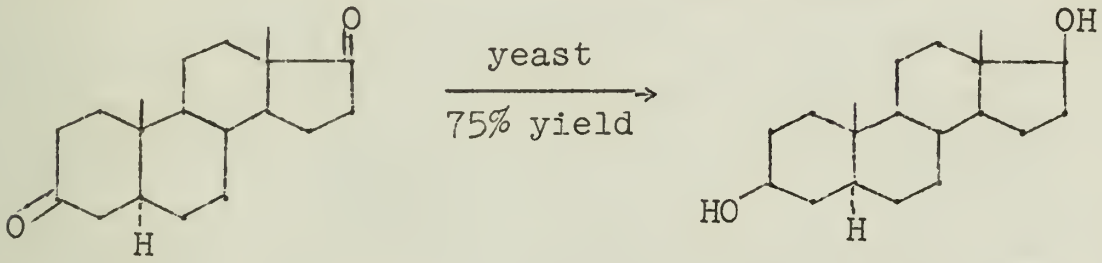
III IV

The concomitant isomerization of the Δ^5 double bond to the Δ^4 compound is quite common in these transformations (see below).

Under anaerobic conditions yeast is capable of reducing carbonyl groups in steroids quite readily. However, the presence of a C-17 side chain quite often inhibits reduction of the C-3 carbonyl group. In addition, compounds lacking a C-17 side chain are usually reduced by yeast only if the carbonyl group is not in conjugation with a double bond. Thus it is possible to selectively reduce Δ^1-androstene-3,17-dione (Va) or Δ^4-androstene-3,17-dione (Vb) to the corresponding C-17 alcohol (1)(44).



On the other hand, androstane-3,17-dione (VII) is completely reduced to the diol (VIII).

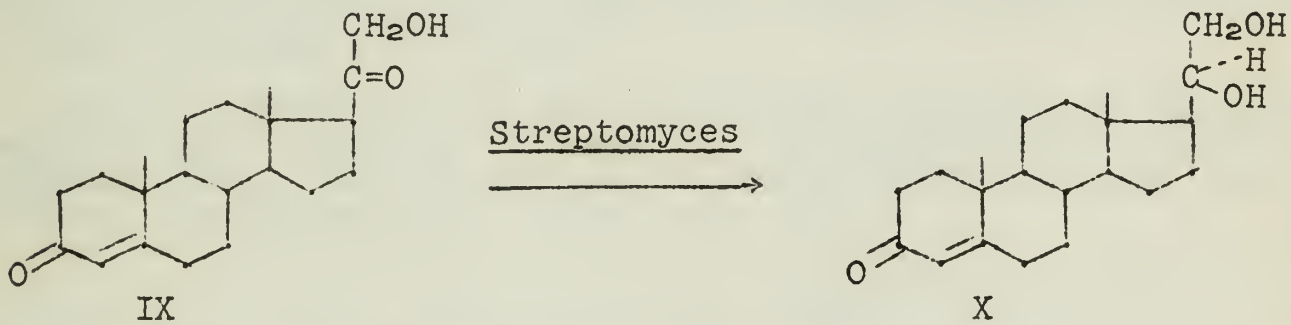


VII VIII

Other workers have demonstrated that exceptions to these generalizations exist (7).

In contrast, in the reduction of carbonyl groups with anaerobic bacteria neither the presence of a C-17 side chain nor of a conjugated double bond inhibits reduction. In fact, in several cases the carbonyl reduction is accompanied by double bond reduction (21)(25).

By means of several different species of mold it has been possible to reduce the C-20 carbonyl group of several steroids, an example being the reduction of deoxycorticosterone (IX) to 20β,21-dihydroxy-Δ^4-pregnene-3-one (X) (9).

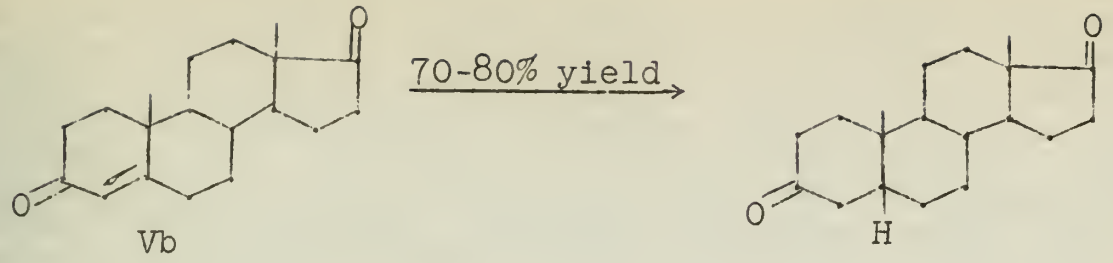


IX X

With similar steroids containing an additional carbonyl group at C-11 it is also possible to accomplish only C-20 carbonyl reduction (14) (26).

II REDUCTION AND FORMATION OF DOUBLE BONDS

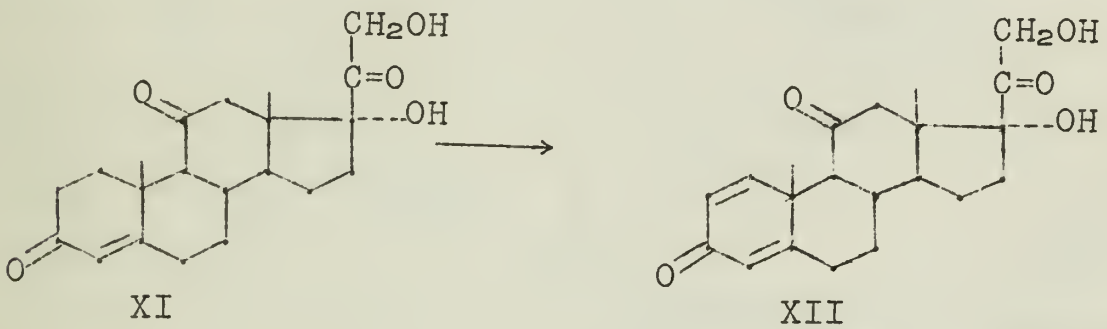
Although simple reductions of double bonds have been accomplished by the use of Bacillus putrificus, as illustrated below for Δ^4-androstene-3,17-dione (Vb) (27),



Vb

the microbiological reaction is of little value to the steroid chemist, since excellent chemical methods are available.

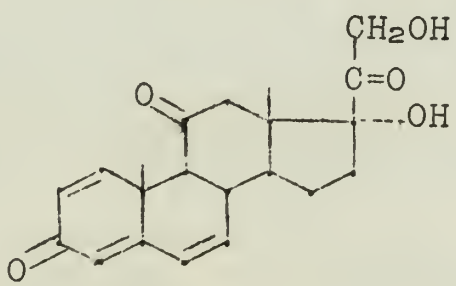
In contrast, the introduction of double bonds by microbial action is a valuable synthetic tool. It is especially important in the cortical hormone field since the 1-dehydro compounds of cortisone and its derivatives have been found to have high physiological activity (28). The main structural requirement appears to be the presence of an oxygen function at C-3. In addition, a 17α-hydroxyl must be present to avoid concomitant side chain cleavage (see next section)(33). This transformation is illustrated with the conversion of cortisone (XI) to 1-dehydrocortisone (XII) and may be accomplished by various species of bacteria or fungi, one of the latter being Didymella lycopersici.



XI XII

Many other steroids, for example, 9α-fluorocortisone, hydrocortisone, and 17α-ethynyltestosterone (III) may likewise be converted to their 1-dehydro analogs (14)(29)(30).

Quite recently it has been found that a species of Bacillus can dehydrogenate 6-dehydrocortisone or 6-dehydrohydrocortisone (1-dehydrocortisol) at C-1 to give, in the case of cortisone, the tri-olefinic derivative (XIII) shown below (31).

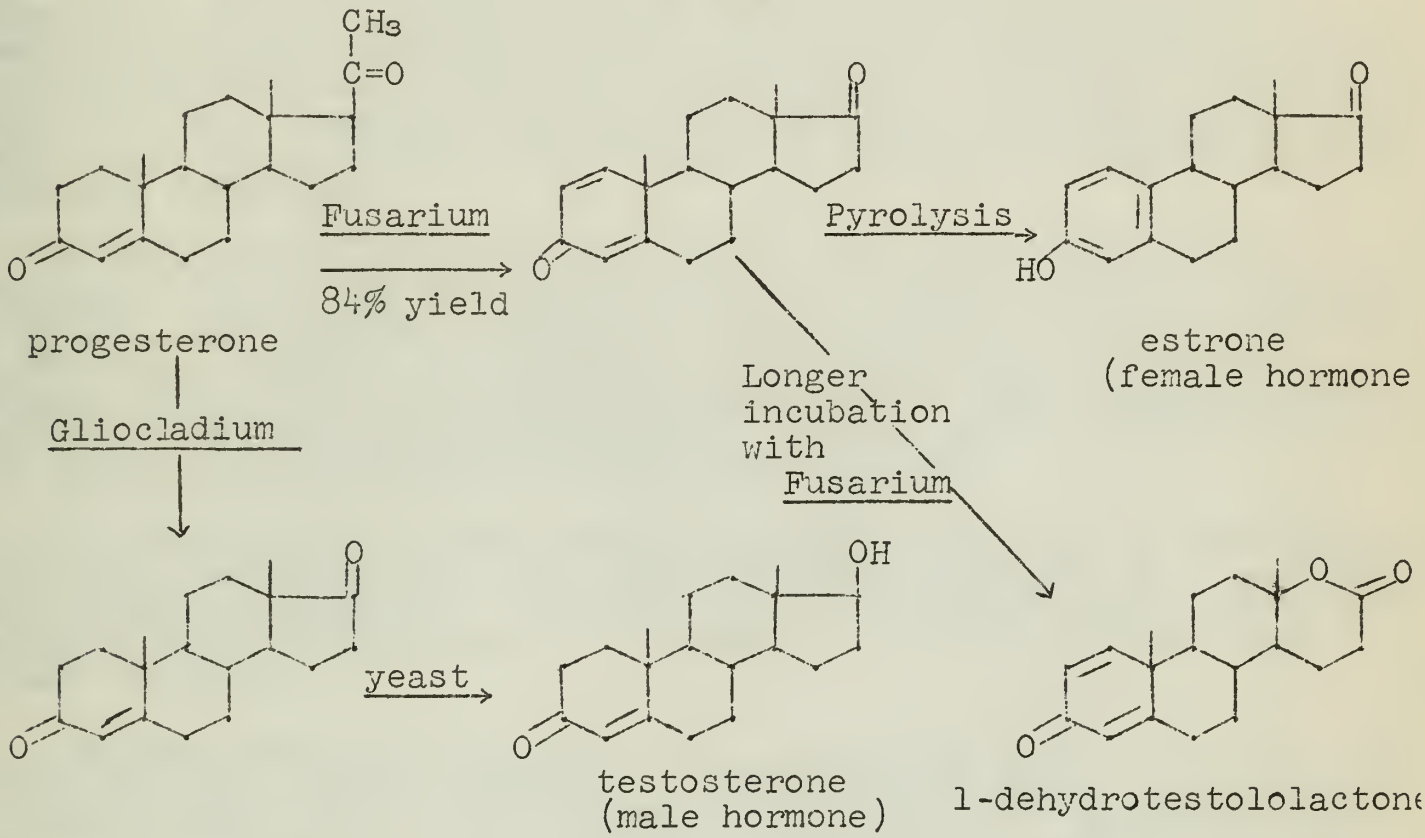


XIII

III SIDE CHAIN CLEAVAGE AND RING CLEAVAGE

Little work has been done on the cleavage of the side chain of C_{27} steroids. It has been shown that when cholestenone is incubated with a species of Proactinomyces a poor yield of the C_{20} acid, 3-keto-4-etienic acid, is obtained (32).

More study has been devoted to the degradation of the side chain of the C_{21} steroids. This degradation produces intermediates that may be converted to the androgenic or estrogenic hormones. With a species of Fusarium concomitant introduction of a double bond at C-1 occurs, and upon longer incubation the D ring is cleaved forming a lactone (33). On the other hand, with species of Gliocladium, Aspergillus or Penicillium only side chain cleavage occurs (34). These transformations, including additional steps which lead to the male and female hormones (1)(33), are illustrated with progesterone as the substrate.

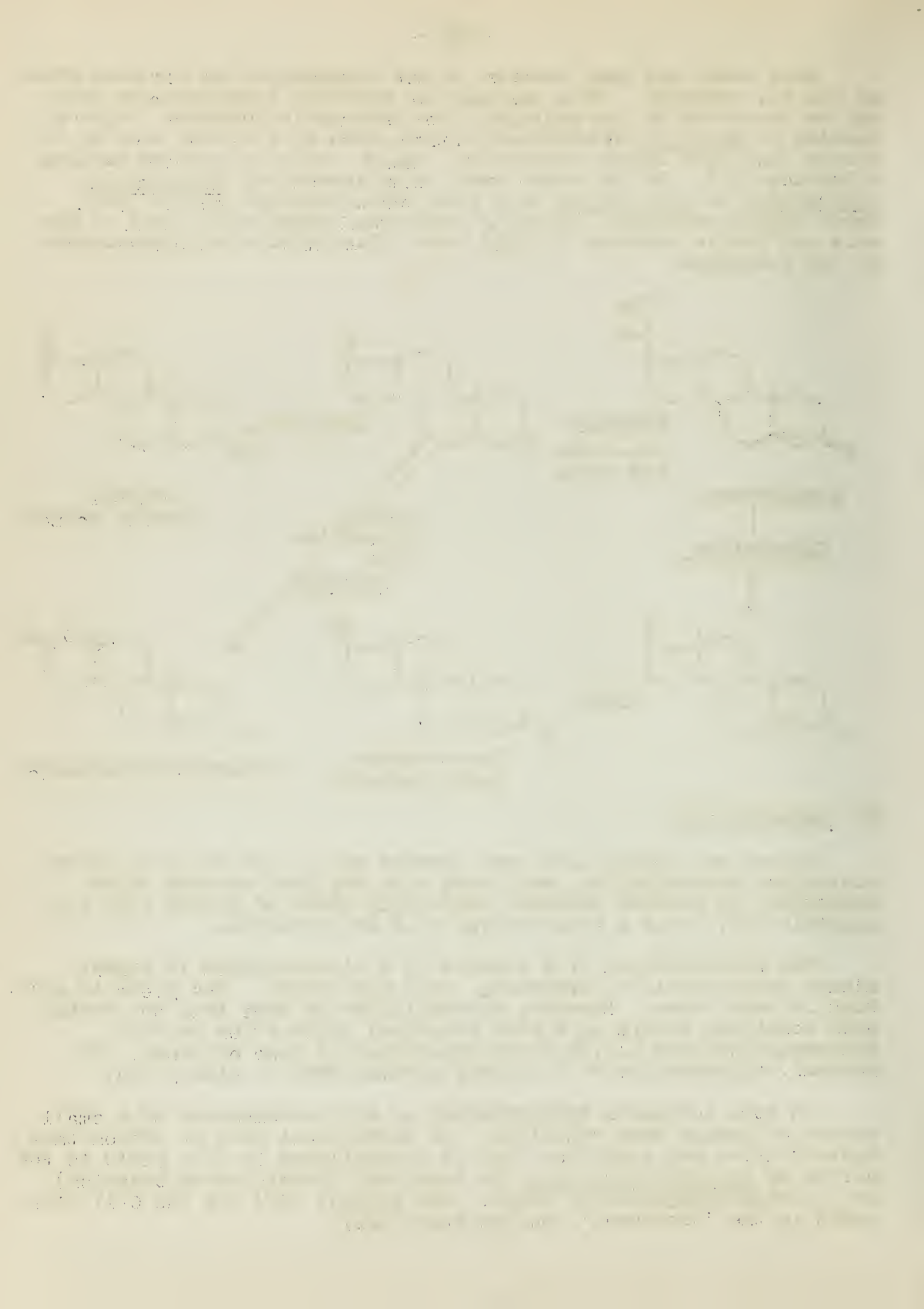


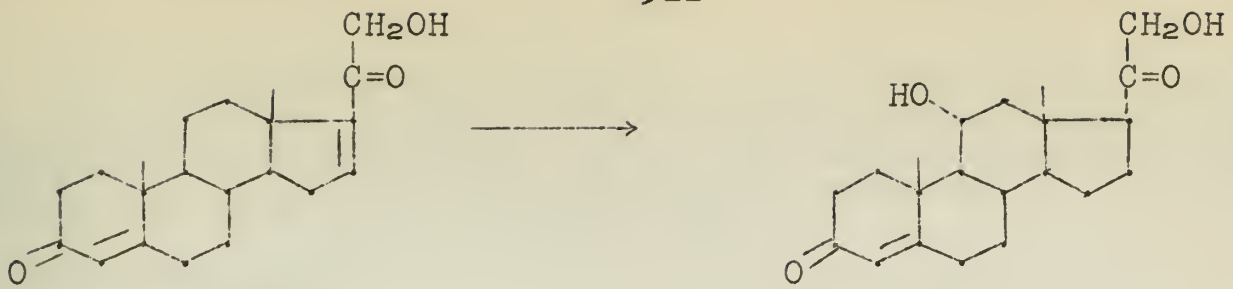
IV HYDROXYLATION

Extensive studies have been carried out in the field of microbiological hydroxylation, and since this has been covered quite thoroughly in several reviews, especially those of Florey (19) and Eppstein (21), only a brief survey will be presented.

The hydroxylation of a steroid by a microorganism is almost always stereospecific, producing only one epimer. The yield is quit high in many cases. However, hydroxylation at more than one carbon atom sometimes occurs as a side reaction; quite often in C-11 hydroxylations the 11α,6β-dihydroxysteroid is also obtained. In general, dihydroxylation is rarely accomplished in high yield.

In some instances hydroxylation is also accompanied by a small amount of double bond reduction. An exceptional case of concomitant hydroxylation and reduction that is accomplished in fair yield is the action of Rhizopus nigricans (an excellent hydroxylating organism) on 16-dehydroprogesterone (XIV). The product (XV) has the C-17 side chain in the 'unnatural' configuration (35).





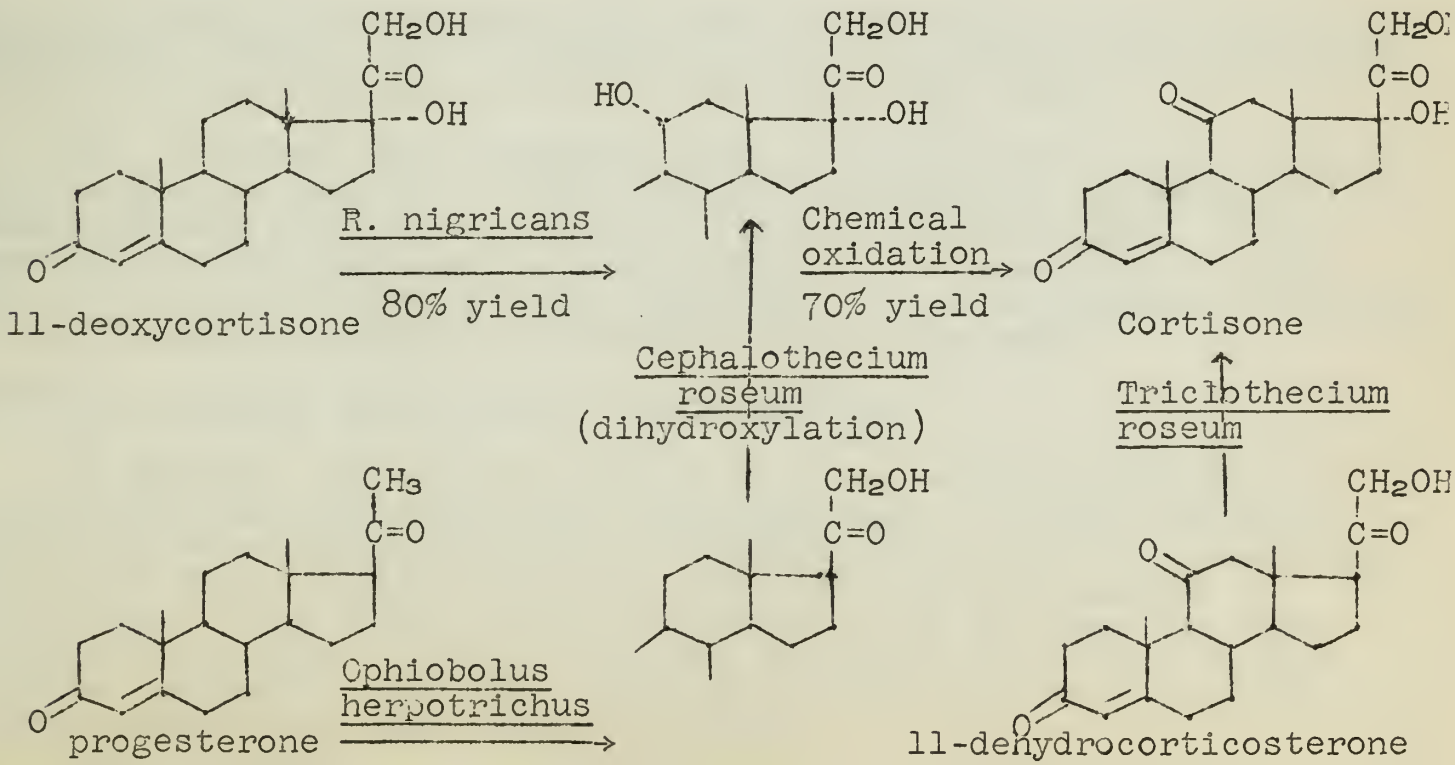
XIV XV

By the use of various microorganisms it has been possible to hydroxylate the 1α,2β,6β,7α,7β,8 or 9 (position and configuration uncertain), 10β,11α,11β,14α,15α,15β,16α,17α, or 21 position of numerous steroids. Whether or not a new steroid can be hydroxylated at a specific position cannot yet be predicted. However, a reasonable choice of which organism to use in the attempted hydroxylation can be made, since the positions hydroxylated by various microorganisms have been well tabulated.

Hydroxylation at the 1α and 2β positions has recently been reported. Incubation of Δ^4-androstene-3,17-dione (Vb) with a species of Penicillium yielded a mixture of the 1α and 2β-hydroxy derivatives of Vb (36). Another mold produced a mixture of the 1€- and 2β-hydroxy derivatives of 11-deoxycortisone (37). When 11-deoxycortisone was incubated with a Streptomyces sp. the sole product isolated (in low yield) was 2β-hydroxy-11-deoxycortisone (38).

An interesting hydroxy derivative, 10β-hydroxy-19-nortestosterone, was prepared in low yield from 19-nortestosterone upon incubation with Rhizopus nigricans. Although the C-10 hydroxyl group was later assigned the β configuration, the proof of this has not been published (39)(16).

Hydroxylation at C-11, C-17, and C-21 is extremely important in adrenocortical hormone synthesis. Hydroxylation at the 11α position is quite common and is often carried out by means of Rhizopus nigricans. This transformation, along with 17α and 21-hydroxylation, is illustrated in the following sequences (40)(41)(42).



While 11β-hydroxylation yields the hydroxyl group in the 'natural' configuration, it has not been as well studied. One organism, Cunninghamella blakesleeana, carries out this hydroxylation quite efficiently, as illustrated with the conversion of 11-deoxycortisone to hydrocortisone in 60-70% yield (43).

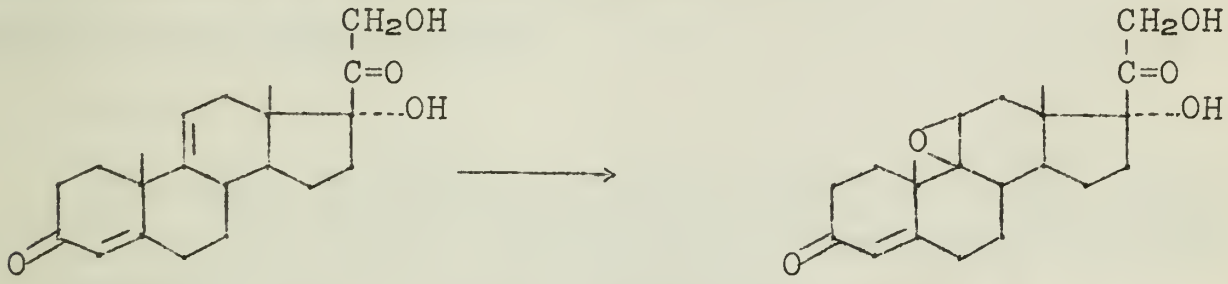
V ESTER HYDROLYSIS

As is generally true for most living organisms, the esterase activity of microorganisms is quite high. This may be exemplified in the case of the hydroxylating microorganism Rhizopus nigricans; when either 21-acetoxy-11-deoxycorticosterone or 11-deoxycorticosterone is incubated with this organism, a 50-60% yield of 11-epicorticosterone is obtained (45).

In the above transformation ester hydrolysis is probably more rapid than the hydroxylation reaction, since no 21-acetoxy-11-epicorticosterone was ever isolated from the incubation mixture.

VI EPOXIDATION

The phenomenon of microbiological epoxidation of steroidal double bonds is extremely interesting when one considers the relative scarcity of epoxide compounds in nature. Thus far two olefin-containing steroids have been reported to be converted to the corresponding epoxides. This has been accomplished by three different organisms, one of them being Curvularia lunata (46).



XVI XVII

Thus, 9-dehydro-11-deoxycortisone (XVI) yields the corresponding 9β, 11β-epoxide (XVII), while 14-dehydro-11-deoxycortisone (XVIII) yields Δ^4-14α-15α-epoxidopregnene-17α,21-diol-3,20-dione (XIX).

The organisms that accomplish these epoxidations are all hydroxylating organisms and produce the 11β and 14α-hydroxyl derivatives when incubated with the saturated analogs of XVI and XVIII. These results rule out the olefins and epoxides as intermediates in 11β and 14α hydroxylations by these organisms, since no enzymatic cleavage of the epoxides to the hydroxy compounds was observed.

PRACTICAL ASPECTS OF MICROBIAL TRANSFORMATIONS

In general, the steroid chemist is interested in carrying out known transformations with known microorganisms. In most cases the microorganisms used in steroidal transformations have been cataloged, and it is often possible to obtain them from various culture collections. Two large culture collections are the American Type Culture Collection (A.T.C.C.) and the Centraalbureau voor Schimmelcultures (Holland). In other cases it is possible to obtain the microorganisms from the original workers.

Although there are many variations in technique, there is one general method of accomplishing steroidal transformations. Since these operations are not generally known to the organic chemist it is worthwhile discussing them in some detail.

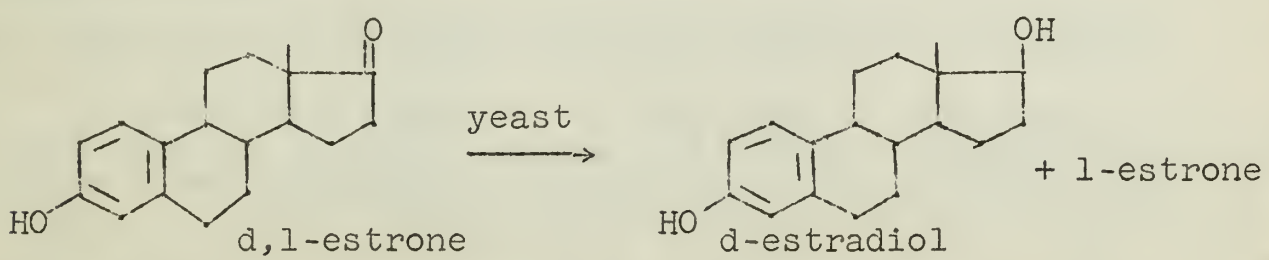
The microorganism is grown in an aqueous solution containing suitable nutrients. Usually the simplest nutrient solution possible is used in order to facilitate the later extraction of the steroid. The microorganism is allowed to grow for periods ranging from 12 hours to several days. Next, either the steroid is added directly to the culture solution or to a buffered suspension of the mycelium. (The mycelium is a fibrous network of growing microorganisms and may be separated from the culture solution by filtration.) The steroid may be added in a water-miscible non-toxic solvent or as a fine powder. The range of maximum permissible concentration of steroid varies with the steroid and the microorganism, but is usually between 0.1 to 1.0 grams per liter. The temperature is maintained between 20-40° depending on the specific transformation, and the container is continuously shaken. In the case of hydroxylations and other oxidations aerobic conditions are maintained, while in reductive transformations anaerobic conditions are usually used. The progress of the transformation may be followed by the use of paper chromatography. After the transformation has been completed (several hours to several days) the usual procedure is to extract the steroids. The steroidal extracts are then chromatographed; both adsorption chromatography on alumina or silica columns and preparative paper chromatography have been used (21)(47)(16)(48).

MECHANISM OF ENZYME ACTION

A. General

Generally, mechanistic studies require isolation of the enzyme(s) involved. This has been accomplished only to a very limited degree in the case of steroid-transforming microorganisms, and hence little is known about the intimate mechanisms.

As mentioned previously, the substrate specificity and stereospecificity of enzyme-catalyzed reactions are very high. The failure of yeast to reduce the C-3 carbonyl group of C-17 side chain-containing steroids is an example of this specificity. Enzymes are also stereospecific in the sense that they will only act on one enantiomorph. Thus, not only may a specific transformation be carried out, but also a racemic mixture may be resolved in the same operation. This is illustrated below (49).



B. Hydroxylation Reactions

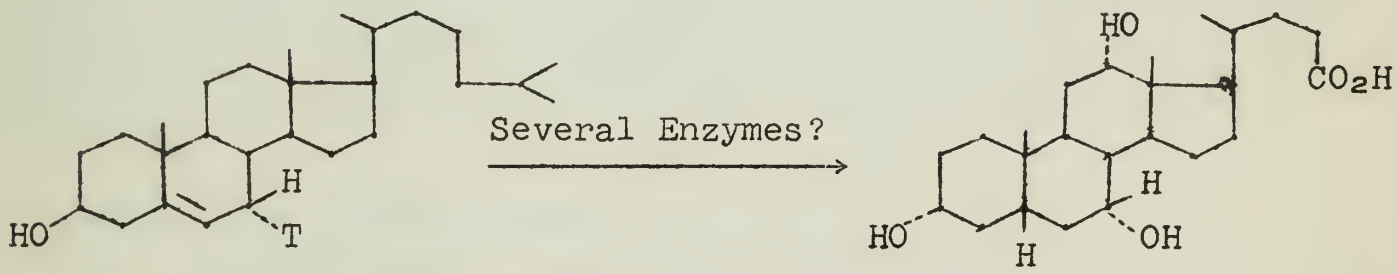
In no reported cases have hydroxylating enzymes been isolated from microorganisms. However, studies on washed cells of a species of Actinomyces has led to the suggestion that adaptive enzymes are

involved in this system (50). When progesterone was incubated with washed cells of Actinomyces sp. eleven hours passed before hydroxylation began. However, when the Actinomyces sp. was grown in the presence of progesterone it rapidly hydroxylated any progesterone later added. Adaptive enzymes have been implicated in the hydroxylation reaction of at least one other microorganism (51).

A possible mechanism for enzymatic hydroxylation is dehydration to an olefin and subsequent hydration. Although in some other biological systems this apparently is the mechanism, it has been disproved in the case of enzymatic hydroxylation of steroids. If olefins were intermediates in the hydroxylation reaction one would expect hydroxysteroids to be produced upon incubation of double bond-containing steroids with the appropriate hydroxylating microorganism. This has not been found (8). Furthermore, incubation of steroids with hydroxylating microorganisms in the presence of D_2O did not result in any incorporation of deuterium. As mentioned previously, epoxides have also been eliminated as intermediates in the hydroxylation reaction.

Other workers have shown that molecular oxygen is the source of the oxygen atom of the hydroxyl group (52), and it has been suggested that the attacking species is a positively-charged enzyme-iron-oxygen complex (53)(15).

Corey and co-workers (54) have shown that at least in mammalian systems the enzymatic hydroxylation proceeds with retention of configuration. When 7α-tritiocholesterol (XV) was fed to a rat the cholic acid (XVI) isolated contained practically no tritium.

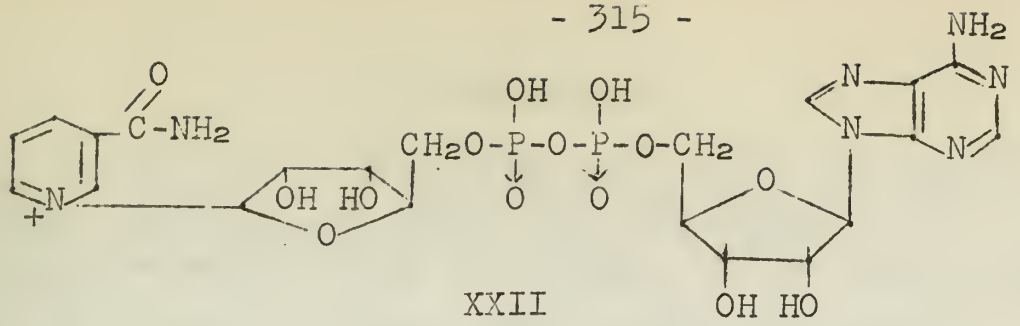


XX XXI

Under identical conditions 7β-tritiocholesterol yielded cholic acid which still contained the major portion of the tritium. These facts are in accord with an hypothesis involving attack by a positive oxygen species.

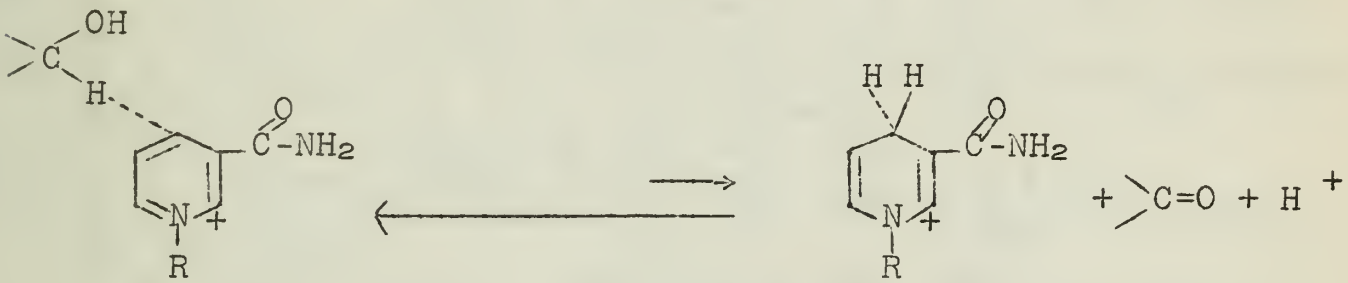
C. Oxidation of Hydroxyl Groups and Reduction of Ketones

Considerable progress has been made in the study of the interconversion of nuclear alcohols and ketones. Talalay has isolated an enzyme from Pseudomonas testosteroni grown in the presence of testosterone (15)(55). This dehydrogenase catalyzes the reversible oxidation of 3β-hydroxysteroids of the C_{19} and C_{21} type, and of 17β-hydroxysteroids of the C_{19} type. The reacting prosthetic group of the enzyme is diphosphopyridine nucleotide (DPN)(XXII).



XXII

The reactions of DPN are well known in enzyme chemistry and have received considerable study. As has been shown for the oxidation-reduction reactions of DPN in other systems (56), the reaction of DPN with hydroxy or ketosteroids involves direct hydrogen transfer (57). The general reaction is



The equilibruim constants for the oxidative reactions when catalyzed by the 3β and 17β-hydroxysteroid dehydrogenase have been determined and were found to be between $1x10^{-9}$ and $40x10^{-9}$ (58). A 3α-hydroxysteroid dehydrogenase has also been isolated (55). This enzyme catalyzes the reversible oxidation of 3α-hydroxysteroids of the C_{19}, C_{21}, and C_{24} (bile acid) types. As expected from a consideration of conformational analysis, the equilibrium constant of the 3α-hydroxysteroid dehydrogenase-catalyzed oxidation (hydroxyl group axial) is larger than that of the 3β-hydroxysteroid dehydrogenase-catalyzed oxidation (hydroxyl group equatorial). The oxidation-reduction reaction when catalyzed by these enzymes may be forced to completion in either direction by application of mass action principles.

D. Double Bond Isomerization

As mentioned earlier, microbial oxidation of the hydroxy group of 3β-hydroxy-$\Delta^{5(6)}$ or $\Delta^{5(10)}$-steroids involves concomitant isomerization of the double bond to yield 3-keto-Δ^4-steroids. While in the case of chemical oxidation (Oppenauer) this isomerization occurs under the reaction conditions, Talalay has shown that in enzymatic oxidations accomplished by P. testosteroni it is catalyzed by a separate enzyme (59). This enzyme has been isolated and has been found to readily catalyze the isomerization of 3-keto-$\Delta^{5(6)}$ or $\Delta^{5(10)}$-steroids to the corresponding 3-keto-Δ^4-steroids. The reaction is essentially irreversible.

It has been suggested that isomerization does not involve olefin hydration followed by dehydration, since when the enzyme catalyzed reaction was run in D_2O or T_2O no isotope was incorporated in a stable position. In contrast, when the acid or base-catalyzed isomerization reaction is run in D_2O incorporation occurs. These results, however, do not rule out the possibility that the enzyme, rather than the solution, donates the elements of water to effect olefin hydration.

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